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New Catalytic Systems with Ionic Liquids as Reaction Media for the Synthesis of Renewable Chemicals

Ph.D. thesis

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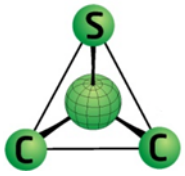
June 2011



Abstract

Producing chemicals from renewable sources is a field that has gained increased attention in recent years. In this connection, ionic liquids (ILs) have proven to be interesting reaction media for the conversion of sugars to platform chemicals. This thesis describes the synthesis of 5-(hydroxymethyl)furfural (HMF) and 2,5-furandiacrboxyl acid (FDA) from carbohydrates in ionic liquids.

In chapter 2 an IL/water system for the enzymatic isomerization of glucose to fructose was demonstrated. The IL *N*,*N*-dibutylethanolammonium octanoate together with 18 wt% water proved to be a benign reaction medium for the enzyme glucose isomerase. In addition to fructose, mannose was formed via the Lobry de Bruyn-van Ekenstein transformation.

Chapter 3 deals with the dehydration of glucose to HMF where new potential catalysts are investigated. Chromium(III) chloride exhibited best performance in imidazolium based ILs with halides as anions. Lanthanide salts also proved to have a catalytic effect for glucose dehydration in alkylimidazolium halides, where ytterbium triflate had the strongest effect. Increasing the alkyl chain length of the imidazolium cation of the IL increased the yield of HMF. In addition to the metal based catalytic systems, boric acid was found to enable synthesis of HMF in 1-ethyl-3-methylimidazolium chloride ([EMIm]Cl), affording HMF in 42 and 66 % from glucose and sucrose respectively. Experimental evidence led to the conclusion that boric acid promoted the isomerization of glucose to fructose, and [EMIm]Cl subsequently mediated the dehydration of fructose to HMF. Calculations with Density Functional theory (DFT) confirmed a decrease in energy for the isomerization pathway when glucose was complexed with boric acid.

Further derivatization of HMF to FDA was investigated in Chapter 4 by the aerobic oxidation in ILs with supported ruthenium hydroxide catalysts. The best yield obtained for FDA was 48 %, using $Ru(OH)_x/La_2O_3$ as catalyst in 1-ethyl-3-methylimidazolium acetate ([EMIm][OAc]) at elevated pressure. Leaching studies showed that the catalyst was not entirely stable under the reaction conditions.

In Chapter 5 an assessment of a process in ILs was made where chemistry, as well as technological and economical parameters, was taken into account. The

assessment concluded that an IL-based process for HMF production is highly dependent on the number of recycles of the IL and the price of the feedstock.

Resumé

Produktion af kemikalier fra vedvarende kilder har fået øget opmærksomhed de seneste år. I denne sammenhæng har ioniske væsker vist sig at være interessante alternativer som reaktionsmedier til omdannelse af sukkere til platformkemikalier. Denne afhandling indeholder en undersøgelse af nye katalytiske system og processer til fremstilling af 5-(hydroxymetyl)furfural (HMF) og 2,5-furandicarboxylsyre (FDA) fra kulhydrater i ioniske væsker. Begge disse stoffer er spået en fremtrædende rolle i fremtidens kemiske industri baseret på fornybare ressourcer.

I afhandlingen er enzymatisk omdannelse af fruktose til glukose undersøgt i forskellige ioniske væsker. Dette har ført frem til identifikation af et velfungerende vand/ionisk væske system, hvor omdannelsen af fruktose fra glukose forløber - dog noget langsommere end i rent vand. Dette er det første eksempel på et velfungerende ionisk væske system for enzymet glukose isomerase.

Til omdannelse af glukose til HMF er der blevet undersøgt en række forskellige nye katalysatorsystemer. Her viste katalysatorer baseret på især lanthanidchlorider og ufarligt borsyre sig specielt interessante som alternativer til eksisterende krom-baserede katalysatorer. En mekanistisk undersøgelse udført med computerberegninger gav indsigt i, hvordan effekten af borsyre opstår og anskueliggjorde hvilken rolle den ioniske væske har.

Ved oxidation af HMF kan dannes FDA, som ventes blive en fremtidig erstatning af monomere i plastfremstilling. Afhandlingen beskriver aerobe oxidationer med ruthenium-katalysatorer i ioniske væsker, og det vises at en god virkningsgrad kan opnås i nogle ioniske væsker ved forhøjet tryk.

Endeligt blev der foretaget en modellering af en fremtidig proces for HMF produktion ud fra glukose indeholdende både økonomiske og proceskemiske parametre. Konklusionen herfra var, at en sådan proces er meget afhængig af prisen af den ioniske væske prisen og dennes genanvendelighed, samt selektiviteten for omdannelsen af glukose til HMF. Samlet set demonstrer arbejdet i denne afhandling mulighederne og begrænsningerne for produktion af HMF i ioniske væsker. Yderligere er der angivet specifikke anvisninger for hvilken fremtidig forskning, der vil være påkrævet på området for at en fremtidig bæredygtig fuldskala pro-

duktion af HMF kan implementeres industrielt.

List of Pulications

Publications included in this thesis

1. T. Ståhlberg, M. G. Sørensen & A. Riisager, Direct conversion of glucose to 5-(hydroxymethyl)furfural in ionic liquids with lanthanide catalysts, *Green Chem.* **2010**, *12*, 321-325

2. T. Ståhlberg, S. Rodriguez-Rodriguez, P. Fristrup & A. Riisager, Metal-Free Dehydration of Glucose to 5-(Hydroxymethyl)furfural in Ionic Liquids with Boric Acid as a Promoter, *Chem. Eur. J.* **2011**, *17*, 1456-1464

3. T. Ståhlberg, W.Fu, J. M. Woodley & A. Riisager, Synthesis of 5-(Hydroxymethyl)furfural in Ionic Liquids: Paving the Way to Renewable Chemicals *ChemSusChem* **2011**, *4*, 451-458

4. A. Boisen, T. Christensen, W. Fu, Y. Gorbanev, T. Hansen, J. Jensen, S. Klitgaard, S. Pedersen, A. Riisager, T. Ståhlberg & J. M. Woodley, Process integration for the conversion of glucose to 2,5-furandicarboxylic acid, *Chem. Eng. Res. Des.* **2009**, *87*, 1318-1327

5. T. Ståhlberg, Woodley, J. M. & Riisager, A. Enzymatic Isomerization of Glucose and Xylose in Ionic Liquids, **2011**, *submitted*

6. T. Ståhlberg, E. Eyjólfsdóttir, Y. Y. Gorbanev & A. Riisager, Aerobic Oxidation of 5-(Hydroxymethyl)furfural in Ionic Liquids with Solid Ruthenium Hydroxide Catalysts, **2011**, *submitted*

7. W. Fu, T. Ståhlberg, A. Riisager & J. M. Woodley, Assessment of Ionic-liquid Process for Synthesis of 5-(hydroxymethyl)furfural from Carbohydrates, **2011**, *submitted*

Miscellaneous publications

1. B. Zeuner, T. Ståhlberg, O. N. van Buu, A. J. Kunov-Kruse, A. Riisager and A. S. Meyer, Dependency of the hydrogen bonding capacity of the solvent anion on the thermal stability of feruloyl esterases in ionic liquid systems, *Green Chem.* **2011**, *13*, 1550-1557

Abbreviations

[BMIm][BF_4]	—	1-Butyl-3-methylimidazolium tetrafluoroborate
[BMIm]Br	—	1-Butyl-3-methylimidazolium bromide
[BMIm]Cl	—	1-Butyl-3-methylimidazolium chloride
[BMIm][PF_6]	—	1-Butyl-3-methylimidazolium hexafluorophosphate
[Bu_3MeN][$MeOSO_3$]	—	Tributylmethylammonium methylsulfate
[Choline][dmp]	—	Choline dimethylphosphate
DBAO	—	*N*,*N*-Dibutylethanolammonium octanoate
DFF	—	Diformylfurfural
DMA	—	Dimethylacetamide
DMF	—	Dimethylformamide
DMSO	—	Dimethylsulfoxide
DOE	—	US Department of Energy
[EMIm]Cl	—	1-Ethyl-3-methylimidazolium chloride
[EMIm][HSO_4]	—	1-Ethyl-3-methylimidazolium hydrogensulfate
[EMIm][MEESU]	—	1-Ethyl-3-methylimidazolium 2(2-methoxyethoxy)ethylsulfate
[EMIm][$MeSO_3$]	—	1-Ethyl-3-methyl imidazolium methanesulfonate
[EMIm][$MeOSO_3$]	—	1-Ethyl-3-methylimidazolium methylsulfate
[EMIm][$N(CN)_2$[	—	1-Ethyl-3-methylimidazolium dicyanamide
[EMIm][OAc]	—	1-Ethyl-3-methylimidazolium acetate
[$EtNH_3$][NO_3]	—	Ethylammonium nitrate
[EMIm][$EtOSO_3$[	—	1-Ethyl-3-methylimidazolium ethylsulfate
EtOAc	—	Ethyl acetate
[$(EtOH)_3$MeN][$MeOSO_3$]	—	Triethanolmethylammonium methylsulfate
FA	—	Formic acid
FDA	—	2,5-Furandicarboxylic acid
GI	—	Glucose isomerase
HAp	—	Hydroxyapatite
HFCS	—	High-fructose corn syrup
[HMIm]Cl	—	1-Hexyl-3-methylimidazolium chloride
HMF	—	5-(Hydroxymethyl)furfural
HMFCA	—	5-Hydroxymethyl-2-furancarboxylic acid
HT	—	Hydrotalcite
LA	—	Levulinic acid
mCPBA	—	*meta*-Chloroperoxybenzoic acid
MIBK	—	Methylisobutyl ketone
[MIm]Cl	—	Methylimidazolium chloride
[MMIm][dmp]	—	Dimethylimidazolium dimethylphosphate

[MMMPz][$MeOSO_3$]	—	1,2,4-Trimethylpyrazolium methylsulfate
NMP	—	*N*-Methyl-2-pyrrolidone
[OMIm]Cl	—	1-Octyl-3-methylimidazolium chloride
OTf	—	Trifluoromethanesulfonate
PET	—	Polyethylene terephthalate

Contents

Abstract **i**

Resumé **iii**

Abbreviations **vi**

Chemicals from Renewables **1**

1.1 Introduction 1

1.2 Biomass Derived Chemicals 3

1.3 The Furanic Platform 8

1.4 Green Chemistry 10

1.5 Ionic Liquids 12

1.6 Aim of Thesis 15

Glucose Isomerization in Ionic Liquids **17**

2.1 Introduction 17

2.2 Enzymatic Isomerization in Various Ionic Liquids 18

2.3 Enzymatic Isomerization in DBAO 20

2.4 Conclusions 24

2.5 Experimental 26

Synthesis of 5-(Hydroxymethyl)furfural in Ionic Liquids **27**

3.1 Introduction 27

3.2 Mechanism of HMF formation 27

3.3 Chromium Catalyzed Synthesis of HMF 29

3.4 Lanthanide Catalyzed Synthesis of HMF 32

3.5 Boric Acid Catalyzed Synthesis of HMF 37
3.6 Miscellaneous Catalysts 44
3.7 Fructose Dehydration in DBAO 45
3.8 Conclusions 45
3.9 Experimental 47

Aerobic oxidations in Ionic Liquids **49**
4.1 Introduction 49
4.2 Oxidation of HMF in [EMIm]Cl 51
4.3 Oxidation of HMF in Various Ionic Liquids 52
4.4 Oxidation of HMF in [EMIm][OAc] at Ambient Pressure 55
4.5 Oxidation of HMF at High Pressure 57
4.6 Conclusions 59
4.7 Experimental 61

Process Development for Production of Biopetrochemicals in Ionic Liquids **63**
5.1 Introduction 63
5.2 Process Design 64
5.3 Assessment of Biphasic HMF Process 66
5.4 Results and Discussion 67
5.5 Purification of HMF 72
5.6 Conclusions 73
5.7 Experimental 75

Conclusions and Future Perspectives **77**

Appendix **87**
7.1 Spectra 87
7.2 Methodology for Process Assessment 96
7.3 Publications 101

Chemicals from Renewables

1.1 Introduction

The scientific achievements of the last two centuries have transformed a preindustrial world into a technologically advanced modern society sustained by an unprecedented energy input. This transformation has made mankind dependent on fossil resources for fuels and chemicals that have become vital to our civilization. The most versatile of these sources is crude oil from which not only transportation fuels are obtained, but also 95 % of all organic compounds that are precursors to important commodities like pharmaceuticals, polymers, solvents and dyes. The inevitable depletion of this natural resource set out a paramount challenge for scientist to replace it with renewable carbon sources.[1–5]

Exact numbers regarding the current state of the world´s oil reserves are difficult to obtain since one has to rely on figures provided by oil companies and governmental organizations that have in their interest not to disclose an impending oil decline. In Figure 1.1 the crude oil production of oil producing countries except the OPEC countries is depicted over time. As can be seen from the graph, most countries reached their peak in oil production around the year 2000 or earlier and are now showing a decline.[6] The exact point in time when peak-oil is reached is a subject of debate, but scientists within the field are in agreement that the peak will eventually be reached at the latest in the middle of this century. Two positions can roughly be distinguished as can be seen in Figure 1.2. The first scenario predicts a historical production of 1.92 trillion barrels of conventional oil with a peak at around the year 2010. The other scenario is that the peak of conventional oil production takes place between the years 2030-2040 with a historical production of 2.93 trillion barrels. In addition to these numbers, ap-

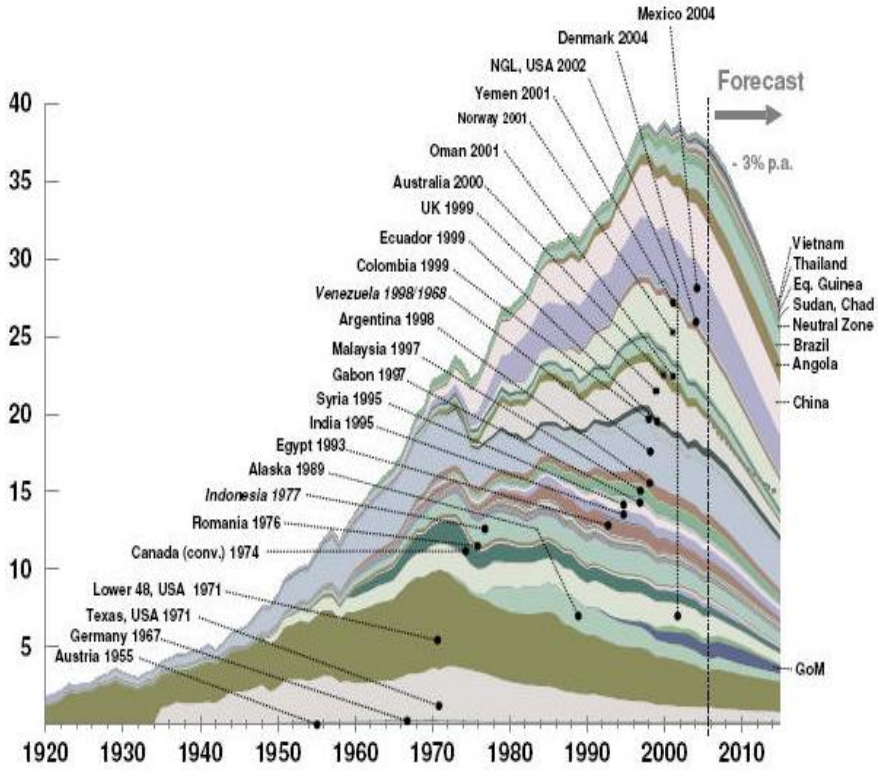


Figure 1.1. Oil production for non-OPEC countries the years 1920-2010.[6]

proximately 0.7 trillion barrels are believed to be produced from unconventional sources such as oil sand and oil shale, which at present are too costly to produce in comparison with conventional sources. Despite the debate over the exact point in time at which the world will run out of cheap oil, scientist within the field are in agreement that the peak is in such proximity that substantial efforts in the scientific community are needed in order to mitigate the transition from a fossil dependent society to one based on sustainable and renewable resources.[6]

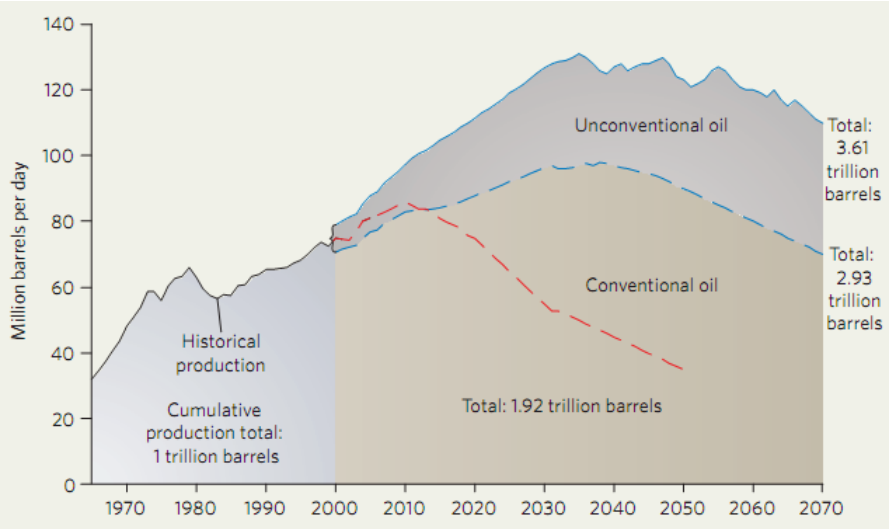


Figure 1.2. The two different scenarios when the peak of oil production is reached.[6]

1.2 Biomass Derived Chemicals

The abovementioned depletion of crude oil does not only have consequences for fuels needed for transportation, it is also a major challenge for our dependence on petroleum derived chemicals. In principal, energy needed for transportation does not by virtue have to be carbon based, whereas the chemicals utilized in our society today for many important applications are organic compounds or derivatives thereof. In this connection, biorefineries, production plants producing chemicals from biomass will come to play a major role. Biomass is a ubiquitous renewable source of carbon that currently has a small part of the world´s chemical production. It has an annual production of $1.8 \cdot 10^{11}$ metric tons of which carbohydrates constitute 75 %.[7] The potential for biomass to replenish the future scarcity of fossil natural resources is enormous. The three most important carbohydrate sources are depicted in Scheme 1.1 and are described briefly below.

1.2.1 Cellulose

Cellulose is a polysaccharide built up by glucose units connected via $\beta(1 \longrightarrow 4)$ glycosidic bonds. It is the backbone of lignocellulose which, in addition to cellulose, consists of the hemicellulose and lignin.[2,7,8] Hemicellulose is a polymer

consisting of several different pentose and hexose sugars where xylose is the most common one. Lignin differs from the first two components by being non-carbohydrate based. It is a polymer consisting of three different aromatic building blocks denoted monolignols. These are *p*-coumaryl alcohol, *p*-coniferyl alcohol and *p*-sinapyl alcohol.[8] A great incentive using lignocellulose as a source for carbon based materials and fuels is that it is non-edible and thus not competing with food. Cellulose make out the largest part of lignocellulose and can be hydrolyzed by inorganic catalysts or by the enzyme catalase to form free glucose. The glucose monomers can subsequently be converted into organic compounds such as succinic acid, lactic acid and hydroquinone. Direct conversion of wood to methanol is achievable by pyrolysis and is considered to be one of the most promising production methods of biofuels with respect to sustainability. Cellulose can also be chemically modified affording interesting materials utilized in e.g. medical technology.[9]

1.2.2 Starch

Starch consists of two glucose polymers denoted amylase and amylopectin. Both are built up by glucose units connected via $\alpha(1 \longrightarrow 4)$ glycosidic bonds and for amylopectin also with $\alpha(1 \longrightarrow 6)$ glycosidic bonds.[7] Starch from corn is used for the production of high-fructose corn syrup (HFCS), a mixture of fructose and glucose used as sweetener in soft drinks.[10] It is also an important source for bioethanol produced by fermentation. As with cellulose, the complete hydrolysis of starch affords glucose monomers which can be further converted into different organic chemicals. Humans posses a group of enzymes called amylases which are responsible for the hydrolysis of starch into maltose, a glucose dimer which is further hydrolyzed to glucose units. The drawback of using starch as a source on large scale for biorefineries is consequently that it is an important food reserve for the human population. A large outtake of starch based resources for chemical production could consequently cause escalation of food prices leading to impoverishment and even starvation.

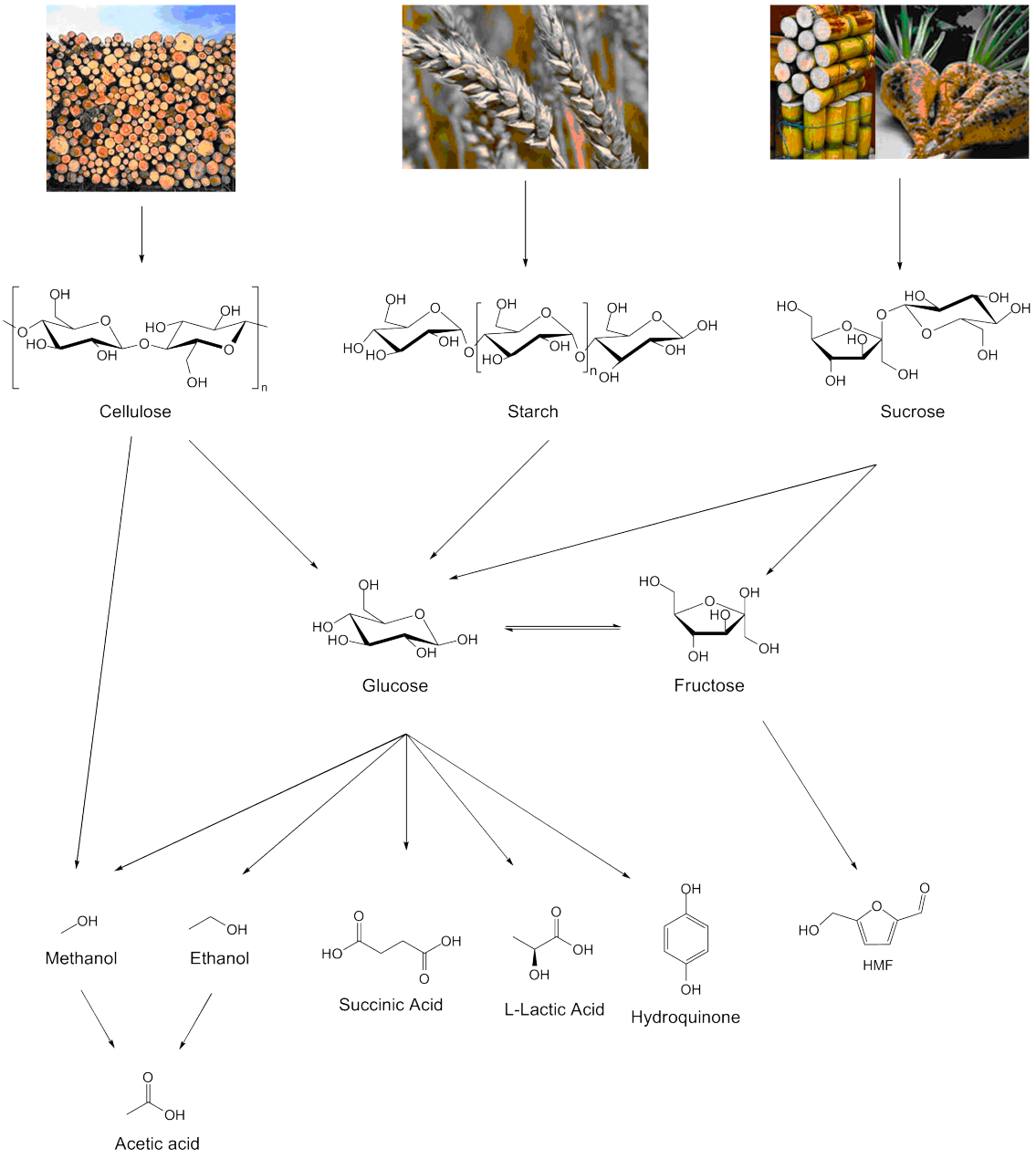
1.2.3 Sucrose

Sucrose is a disaccharide consisting of one glucose unit and one fructose unit connected via a glycosidic bond. It is produced primarily from sugar beet and sugarcane with an annual production of $1.7 \cdot 10^8$ metric tons and has its most common use in the production of food and beverages.[7,11] The currently most important non-food application is the production of ethanol by fermentation, an important transportation fuel in Brazil. Other compounds produced by fermentation of sucrose are amino acids and hydroxy acids.[7]

1.2.4 Other Renewable Sources

In addition to the renewable sources described above a few more deserve mentioning. Inulin is a polymer consisting of fructose monomers bound together with $\alpha(1 \longrightarrow 2)$ glycosidic bonds with a glucose unit in the reducing end. It is an energy reservoir for some plants e.g. Jerusalem artichoke and suitable as feedstock for chemicals derived from fructose.

Other important renewable sources for the production of fuels or chemicals are vegetable oils and animal fat. These consist of triglycerides which can be converted into fatty acids, glycerol or biodiesel. Glycerol is considered to be a very important building block from which chemicals like 1,2- and 1,3-propanediol, glycerol carbonate and dihydroxyacetone can be derived.[2]



Scheme 1.1. Examples of routes to commodity chemicals from the three major carbohydrate sources cellulose, starch and sucrose.

1.2.5 The Renewable Chemical Industry

Building a new chemical infrastructure can proceed via two different strategies. The first strategy is to produce renewable platform chemicals identical to the current chemicals produced from crude oil. These can be e.g. acetic acid and ethylene from bioethanol, acrolein from glycerol and hydroquinone from glucose. The other strategy is building up a chemical infrastructure based on platform chemicals less common today, but readily derived from biomass. These can be

e.g. lactic acid from glucose, 5-(hydroxymethyl)furfural (HMF) from fructose (or glucose), furfural from xylose and 1,3-propanediol from glycerol. An overview of the two strategies can be seen in Figure 1.3.[3] In 2004 the US Department of

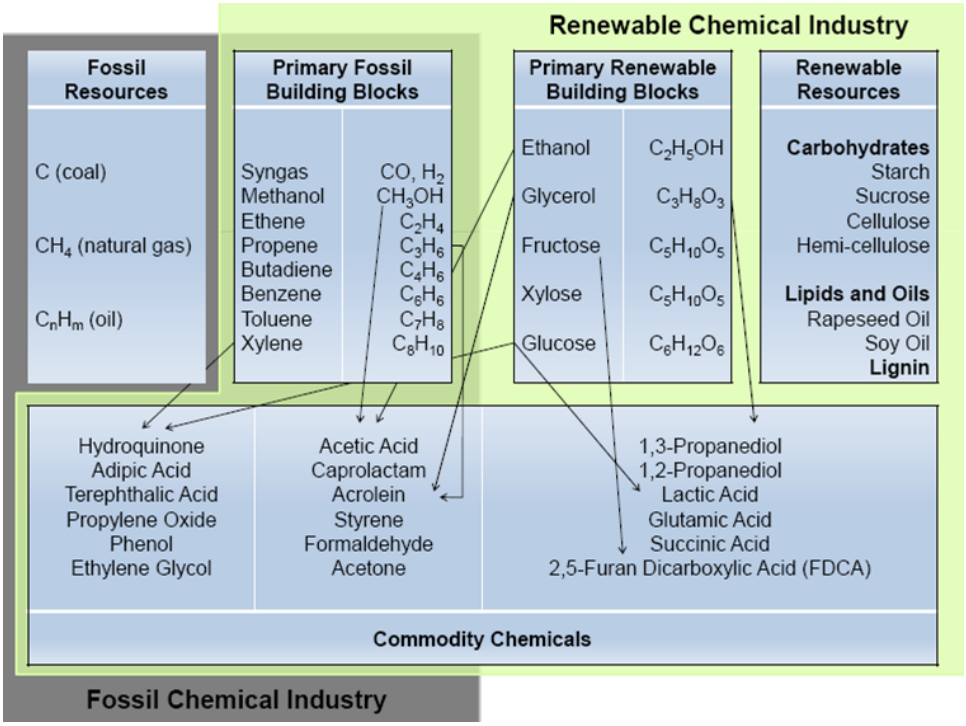
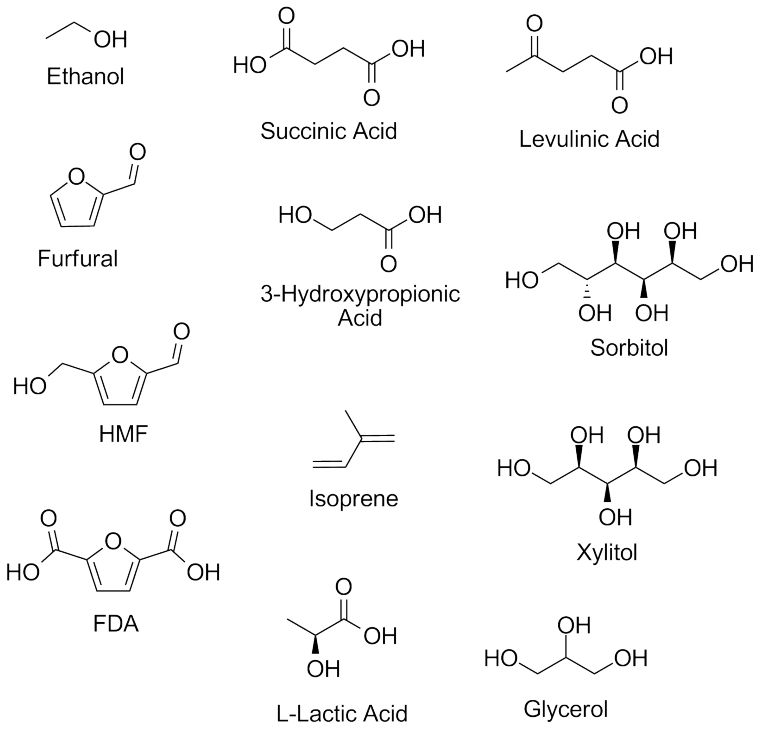


Figure 1.3. Different strategies for producing commodity chemicals.[3]

Energy (DOE) released a document where ten compounds were defined as particularly important to pursue for future biorefineries.[1] This report was recently updated[5] and the compounds declared as potential platform chemicals are shown in Scheme 1.2.

All compounds depicted in Scheme 1.2 have received significant attention in the scientific literature, which was also one of the main criteria for the list.[5] Another important criterion stipulated was that the chemicals should have a broad potential as platform chemicals leading to many different derivatives and applications. This criterion was met by nearly all and it particularly applies to compounds like HMF, levulinic acid and glycerol.



Scheme 1.2. Top Value Added Chemicals.[1,5]

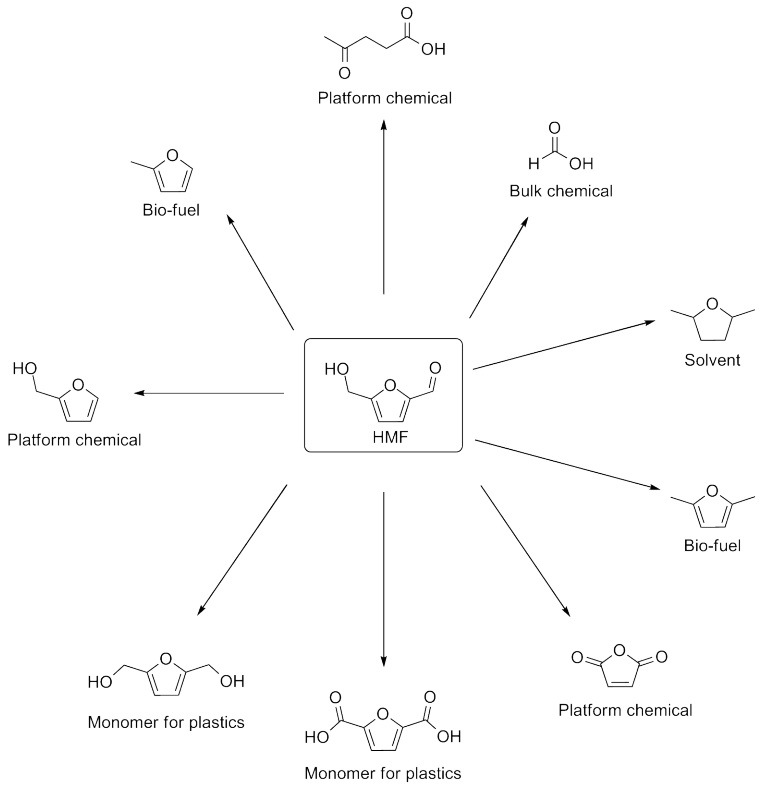
1.3 The Furanic Platform

The abovementioned HMF, a furan derivative formed by the triple dehydration of hexoses, was in the first DOE report only mentioned as an intermediate for the production of 2,5-furandicarboxylic acid (FDA) and levulinic acid.[1,12] It has later been recognized as more important since it can work as an intermediate for a plethora of compounds for several different applications, making it a platform chemical in its own right.[5] The primary target of HMF is nevertheless still considered to be FDA, which is believed to be a possible replacement for terephtalic acid as monomer in polyethylene terephthalate (PET).[1,13,14] Reduction of the furan ring would yield compounds suitable as solvents or fuels.[15]

The first synthesis of HMF was reported as early as the late 19$^{\text{th}}$ century by Düll and Kiermayer independently.[16,17] The synthesis of HMF has then been developed and tested in various solvent systems throughout the 20$^{\text{th}}$ century without leading to any commercialization of large scale processes.[12,18,19] The reaction has been studied extensively in water solutions,[20–29] even though it suffers from poor selectivity in aqueous conditions due to the irreversible hydrolysis of HMF to formic acid and levulinic acid.[30,31] This can to some extent be circumvented

by employing biphasic systems allowing the formed HMF to be continuously extracted by an organic solvent and thus limiting hydrolysis.[15,32,33] The drawbacks of aqueuos conditions can be avoided in aprotic high-boiling solvents,[34–40] where the highest yields are obtained in DMSO. However, difficulties with recovery of HMF from high-boiling solvents makes them less attractive for large scale processes.[36] In addition to the problem of irreversible hydrolysis, the dehydration also suffers from polymerization of sugars and intermediates within the reaction sequence. The polymers formed are denoted humins or humic acids and their formation increases with the concentration of the reacting sugar.[31,41] Humins are formed in all solvents, but varies in extent dependening on the selectivity of HMF formation.

Examples of interesting derivatives produced from HMF in addition to FDA are depicted in Scheme 1.3.[12,14,42,43] The previously mentioned levulinic acid is considered as a platform chemical for solvents or fuels, while the other hydrolysis product, formic acid, is common bulk chemical. Complete reduction of HMF to dimethylfuran, a possible fuel or solvent, can be achieved with a copper/ruthenium catalyst. A recent publication showed that HMF could be directly oxidized to maleic anhydride,[44] a compound normally derived from succinic acid which could work as a precursor to fumaric and maleic acid.[5]



Scheme 1.3. The Furanic Platform.

1.4 Green Chemistry

A chemical infrastructure based on renewable resources is not the only requirement for the future chemical industry. The concept of *Green Chemistry* was introduced by Anastas[45] in 1998 and has since then become a leading guide for the development of chemical processes in all segments of the industry. In principal, it consists of 12 points that should be pursued whenever a new process is being developed or updated in order to assure sustainability and minimize environmental impact:

1. Prevention - It is better to prevent waste than to treat or clean up waste after it has been created.

2. Atom Economy - Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. Less Hazardous Chemical Syntheses - Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

4. Designing Safer Chemicals - Chemical products should be designed to effect their desired function while minimizing their toxicity.

5. Safer Solvents and Auxiliaries - The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

6. Design for Energy Efficiency - Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. Use of Renewable Feedstocks - A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. Reduce Derivatives - Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9. Catalysis - Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. Design for Degradation - Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. Real-time analysis for Pollution Prevention - Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. Inherently Safer Chemistry for Accident Prevention - Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

In order to follow the points above, general methods to measure the 'greenness' of a process are needed. For points 1, 2, 8 and 9 an important measurement is the amount of waste produced per kilogram of product. This can be derived by the so called E-factor introduced by Sheldon.[46] The E-factor is defined as follows:

$$\text{E-factor} = \frac{\text{kg waste produced}}{\text{kg product produced}}$$

The challenge of reducing waste is dependent on the type of industry. In Table 1.2 the amount of waste produced from different industry segments is shown. The pharmaceutical industry is by far the most waste producing segment as a consequence of the complexity and application of its products. The bulk chemical industry, on the other hand, consists to a large extent of products, the processes of which have been developed, not only by mere demand, but also because they are easily obtained from crude oil.

Table 1.2: The E-factor for different industry segments

Industry segment	Product tonnage	kg byproduct/kg product
Bulk chemicals	$10^4 - 10^6$	$< 1 \rightarrow 5$
Fine chemicals	$10^2 - 10^4$	$5 \rightarrow > 50$
Pharmaceuticals	$10 - 10^3$	$25 \rightarrow > 100$

A supplement to the E-factor is the climate factor or the C-factor introduced by Christensen,[3] whereby the amount of CO_2 produced is taken into account for a chemical process, providing a number that reveals its renewability:

$$\text{C-factor} = \frac{\text{kg } CO_2}{\text{kg product produced}}$$

This can be related to points 6 and 7 in Anstas´ 12 principles of green chemistry.

1.5 Ionic Liquids

In connection to green processes, ionic liquids (ILs) are interesting alternatives to conventional molecular solvents due to their negligible vapor pressure, non-flammability and unique dissolving abilities for polar compounds and polymers.[47] The increasing demand for sustainable and green chemical processes has led to a substantial increase in the research concerning ILs.

ILs are commonly defined as salts that are liquid below 100 °C. The first known example in literature is from 1914 when Paul Walden observed ethylammonium nitrate ($[EtNH_3][NO_3]$ to have melting point of 13-14 °C.[48] In the years to follow, very few examples appeared that built on Walden´s discovery and it was not until the beginning of the next century that the science of ILs would take its giant leap. As can be seen Figure 1.4, a very modest number of publications concerning ILs in the early 1990s has virtually exploded in the past decade. Significant discoveries concerning catalysis,[49,50] pharmaceuticals,[51] electrochemistry,[52] organic synthesis,[53] inorganic synthesis[54] and polymer synthesis[55] have been made and industrial applications are already a reality.[56]

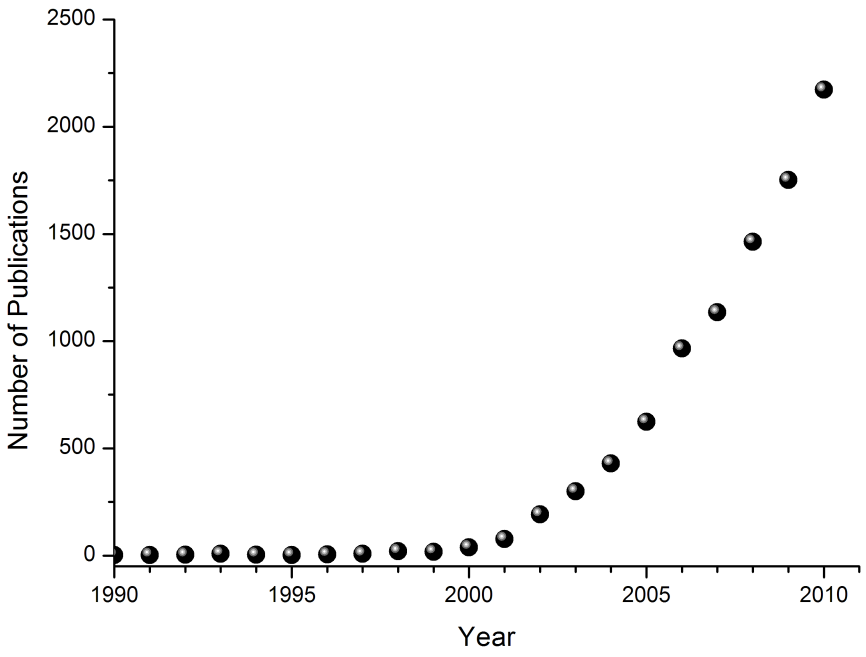


Figure 1.4. Number of publications on ILs since 1990.

Combining different anions and cations give an almost infinite variation of ILs. The most common cations and anions for ILs are shown in Figure 1.5 and Figure 1.6. A common method of synthesizing ILs is a by the Menshutkin reaction where a tertiary amine is reacted with an alkyl halide to yield a quaternary ammonium salt. This method provides so-called first generation ILs such as 1-ethyl-3-methylimidazolium chloride ([EMIm]Cl) and 1-butyl-3-methylimidazolium chlo-

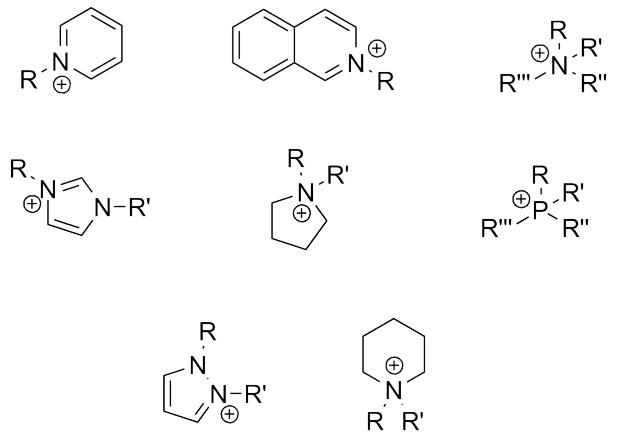


Figure 1.5. Common cations for ionic liquids.

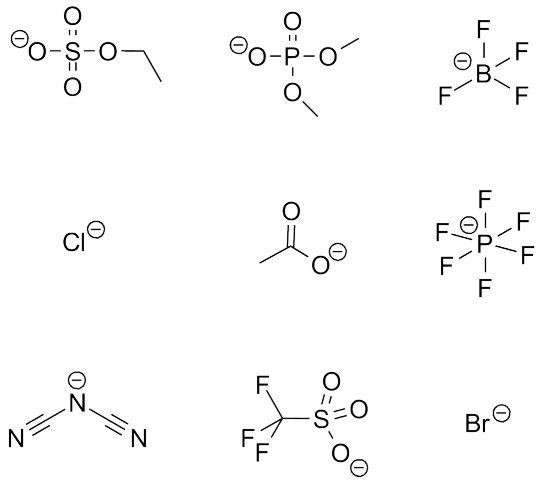


Figure 1.6. Common anions for ionic liquids.

ride ([BMIm]Cl). These can be reacted further to afford second generation ILs via the Finkelstein reaction. This is achieved by reacting the quaternary ammonium halide with salts such as $NaBF_4$ or $NaN(CN)_2$, exchanging the halide with BF_4^- or $N(CN)_2^-$. Examples of second generation ILs are 1-ethyl-3-methylimidazolium tetrafluoroborate ([EMIm][BF_4]) and 1-ethyl-3-methylimidazolium dicyanamide ([EMIm][$N(CN)_2$]).

Given their unique abilities, ILs are often denoted as 'green solvents', something which is a rough generalization. Even though many ILs fit in to the description of being green, many have shown high toxicity values towards aquatic life forms making them undesirable on a larger scale.[57,58] Nevertheless, this issue can be circumvented by minimizing the amount of IL entering water waste streams and designing processes where the IL is recycled and the desired product

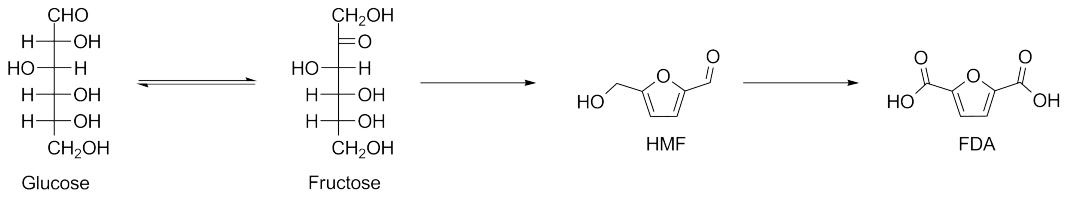
efficiently removed. Another benefit towards molecular solvents is their negligible vapor pressure which minimizes the exposure to workers and the atmosphere. The common denotation of ILs as 'green solvents' should therefore only be used if the specific application of an IL can be regarded as green.

Unique dissolving abilities for biopolymers make ILs particularly interesting as media in biorefineries. Certain ILs have dissolved as much as 25 wt% of crystalline cellulose,[59–61] and few of them have proven to be highly advantageous in the production of HMF from fructose and glucose.[42,43] In particular [EMIm]Cl and [BMIm]Cl form HMF with high selectivity from fructose and, with the addition of an appropriate catalyst, also from glucose.[62–64] Humin formation remains a problem for HMF synthesis in ILs, but can be significantly reduced as the selectivity for HMF is very high in many reaction systems. The combination of ILs and their ability to dissolve biomass together with the high selectivity for hexose dehydration opens up an opportunity for one-pot reactions from cellulose to HMF and in theory even further to its possible derivatives e.g. via subsequent hydrogenation and oxidation.

1.6 Aim of Thesis

The aim of this thesis was to develop new catalytic systems for the synthesis of HMF and its further oxidation to FDA in combination with ILs. The complete reaction sequence is depicted in Scheme 1.4, and feedstock includes hexose sugars as well as sucrose and polymers of glucose like cellulose and starch. Included in the synthetic path of glucose to HMF is the isomerization of glucose to fructose, which can be made enzymatically or with inorganic catalysts. The isomerization step is covered in Chapter 2, where the possibility of performing an enzymatic conversion of glucose to fructose in ILs was investigated. The most challenging step is the dehydration of hexoses to HMF, both in terms of controlling selectivity for the reaction as well as essential process steps such as work up and purification. The work presented in this thesis therefore focused on this step, which is described in Chapter 3. The investigation also had the ambition of meeting the principles of green chemistry, e.g. catalytic oxidations using dioxygen as bulk

oxidant in the last step. The oxidation of HMF in ILs is presented in Chapter 4. To complete the work, an attempt to cost a possible HMF process in ILs was made. The development of HMF production at scale is covered in Chapter 5.



Scheme 1.4. The aim of this thesis was to develop new catalytic systems for the synthesis of HMF and FDA from biomass in connection with ILs.

Glucose Isomerization in Ionic Liquids

2.1 Introduction

The first crucial step within the furanic platform reaction sequence is the isomerization of glucose to fructose. The desired platform chemical HMF is readily obtained from the ketohexose fructose at elevated temperatures, whereas the aldohexose glucose requires a special catalyst to attain acceptable yields. An integrated process for the enzymatic isomerization of glucose to fructose followed by the subsequent dehydration of fructose to HMF would therefore be advantageous. Ideally, the dehydration of fructose to HMF would take place in an IL system that worked for the enzymatic isomerization of glucose, thus consuming the formed fructose during the course of reaction by the formation of HMF.

Since the beginning of this millennium, enzymatic reactions have been widely studied in ILs.[65,49] Especially lipases have shown to uphold stability and exhibit retained or even improved activity in ILs.[66–73] Other important studies include the synthesis of aspartame with thermolysin in 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIm][PF_6])[74] and interesting results concerning biomass obtained with cytochrome c in hydrated ionic liquids.[75,76]

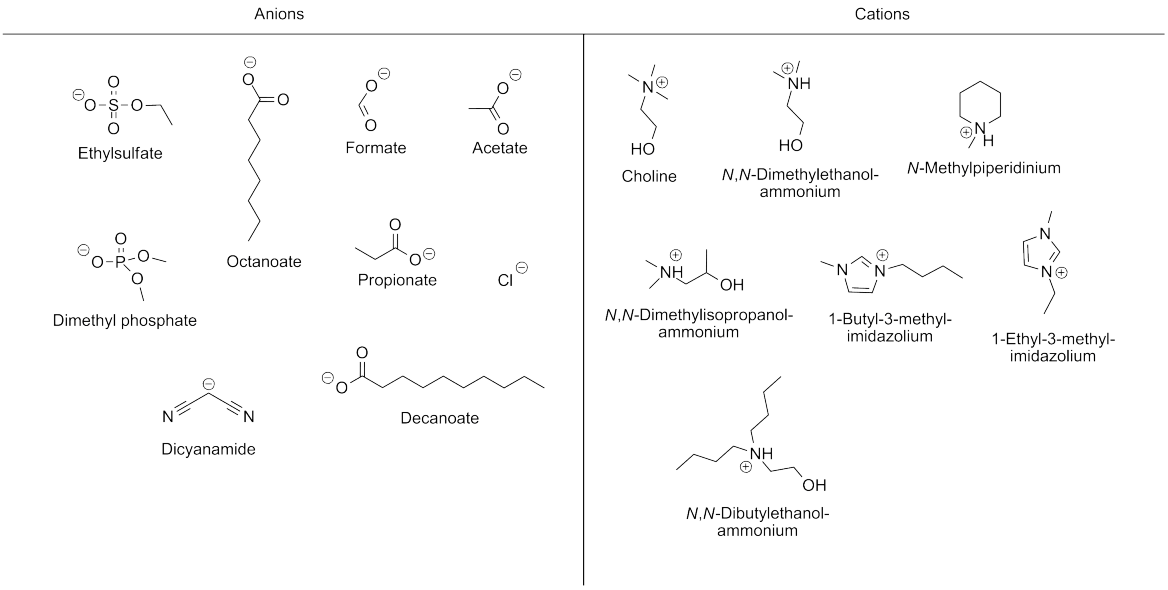
Glucose isomerase (GI) is a xylose isomerase and catalyzes in nature the isomerization of xylose to xylulose. Its active site is built up by a binuclear magnesium ion to which the sugar is bound facilitating the hydride transfer of a proton from C2 to C1.[77] In spite of being a xylose isomerase, it is used industrially for the isomerization of glucose to fructose where its main use is the production of HFCS (see Chapter 1) which at present belongs to the most important indus-

trial bioprocesses. The yield of fructose in the isomerization is approximately 50 % depending on the temperature. This thermodymanical limitation makes a chromatographic step necessary in order to increase the ratio of fructose.[10] Enrichment of fructose can also be achieved by the addition of compounds forming esters with the sugar such as boric acid and germanate ions, but these methods are not applicable on a large scale.[78,79] In the industrial processes GI is exclusively used in its immobilized form. Our work was made with Sweetzyme, a GI derived from a strain of the bacterium *Streptomyces murinus* and immobilized by the crosslinking of whole cells with glutarealdehyde.[80]

2.2 Enzymatic Isomerization in Various Ionic Liquids

The screening of GI involved primarily ILs obtained from CLEA Technologies which had proven to be particularly benign to enzymes. In addition to this, ILs suitable for fructose dehydration ([EMIm]Cl and [BMIm]Cl) were chosen since these would be the ones most likely to enable an efficient one-pot reaction to HMF. Other ILs tried were [EMIm][$N(CN)_2$], an IL with the ability to dissolve biomass in large amounts[81] and [EMIm][$EtOSO_3$], an IL considered to be particularly environmentally benign.[47] Examples of the ions of the ILs can be seen in Scheme 2.5.

The isomerization attempts were made in pure IL (where dissolution of sugar and $MgSO_4$ was possible) and with 9 wt% and 18 wt% of H_2O. In addition, $MgSO_4$ was used as additive in each experiment, a requirement since the active site of glucose isomerase consists of a binuclear magnesium ion. The results are shown in Table 1. The desired ILs for fructose dehydration, [EMIm]Cl and [BMIm]Cl, appeared to have detrimental effect on the enzyme and neither fructose nor HMF was detected when employing these ILs as solvents. Longer reaction times only resulted in humin formation. Neither [EMIm][$N(CN)_2$] nor [EMIm][$EtOSO_3$] showed any conversion to fructose, and like the imidazolium chlorides exhibited humin formation after longer reaction times. The screening with the IL kit from CLEA Technologies gave some successful conversions



Scheme 2.5. Examples of different anions and cations of the ILs used in the initial screening of enzymatic glucose isomerization.

of glucose to fructose. As can be seen from Table 2.3 most ILs had very low conversion and only *N*,*N*-dibutylethanolammonium octanoate (DBAO) showed real promise for future investigations. It was obvious that ethanolammonium carboxylates were the most benign ILs indicating that the hydroxyl group had a stabilizing effect for enzyme activity.

Table 2.3: Isomerization of glucose to fructose in ILs with Sweetzyme at equilibrium.[a]

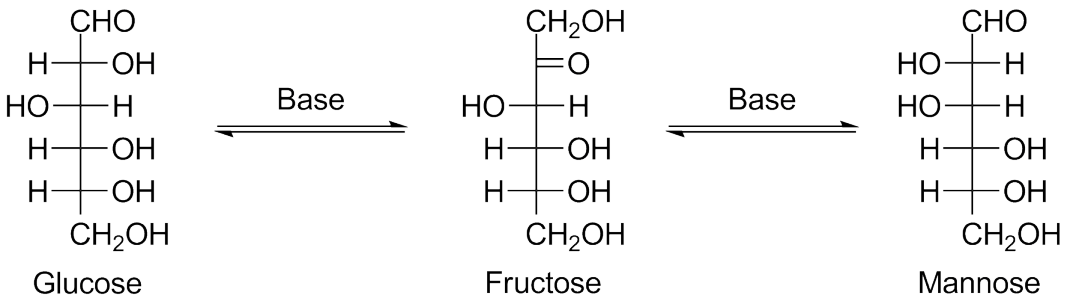
		Glucose:Fructose ratio (mol:mol)		
Entry	Ionic Liquid	No H_2O	9 wt% H_2O	18 wt% H_2O
1	*N*,*N*-Dimethylethanolammonium formate	N/A	95:5	94:6
2	*N*,*N*-Dimethylethanolammonium propionate	N/A	77:23	83:17
3	*N*,*N*-Dimethylethanolammonium decanoate	N/A	82:18	86:14
4	Choline propionate	N/A	96:4	95:5
5	*N*,*N*-Dimethylbutylammonium propionate	N/A	N/A	87:13
6	*N*-Methylpiperidinium acetate	N/A	99:1	91:9
7	DBAO	N/A	N/A	46:52[b]
8	*N*,*N*-Dimethylisopropanolammonium propionate	80:20	82:18	89:11
9	Choline acetate	94:6	95:5	94:6
10	[EMIm][OAc]	95:5	95:5	95:5
11	[BMIm][OAc]	94:6	94:6	93:7
12	*N*,*N*-Dimethylethanolammonium formate	N/A	95:5	94:6

[a] Reaction conditions: 100 mg glucose, 0.8-1.0 g IL, 0-0.2 mL H_2O, 30 mg Sweetzyme and 3.3 mg $MgSO_4 \cdot 7H_2O$, 60 °C, 24 h. [b] 2 % mannose present

2.3 Enzymatic Isomerization in DBAO

Isomerization was investigated further in DBAO using different temperatures. The least amount of water possible was 18 wt% in order to form a clear solution with glucose. The temperatures chosen were 60, 70 and 80 °C, which is around the optimum temperature for the enzyme in water.[10] Temperature is affecting the thermodynamics, and the equilibrium is shifted towards fructose when increasing the temperature.

The isomerization of glucose in DBAO at 60 °C is shown in Figure 2.7. As can be seen from the graph about 25 % of fructose was formed after one hour which was significantly slower than the control experiment in water. After 4 hours over 50 % was formed and leaving the reaction for another 24 hours resulted in a fructose yield of 52 %. In addition to fructose, 2 % of mannose was formed after 24 hours and continued to increase resulting in a yield of 5 % after 72 hours. This was most likely a consequence of the Lobry de Bruyn-van Ekenstein transformation which is the base catalyzed epimerization of aldohexoses to ketohexoses and vice versa (Scheme 2.6).[82]



Scheme 2.6. Lobry de Bruyn-van Ekenstein transformation is the base catalyzed isomerization of aldohexoses to ketohexoses and its reverse reaction. Here exemplified with glucose, fructose and mannose

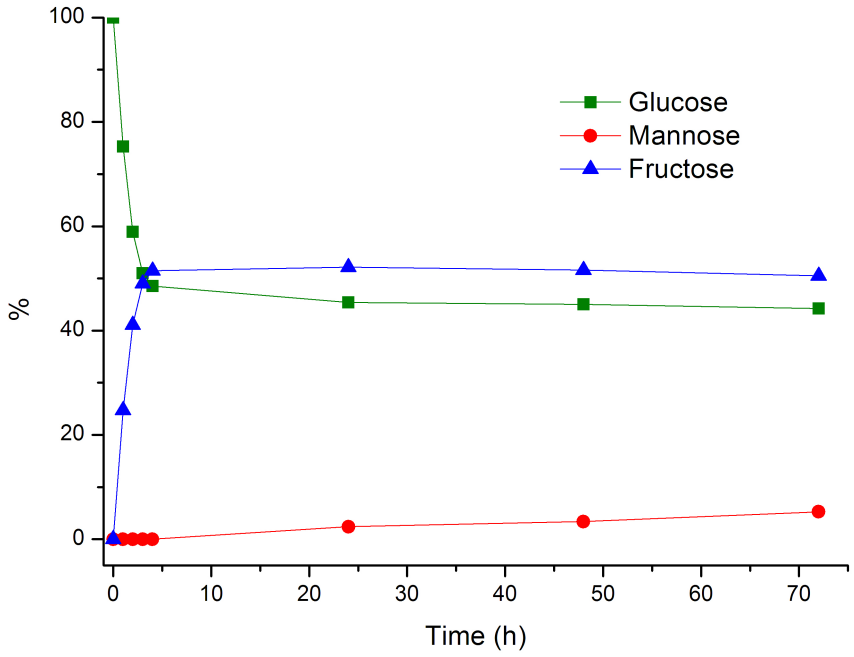


Figure 2.7. Enzymatic conversion of glucose to fructose in DBAO at 60 °C. Reaction conditions: 100 mg glucose, 0.8 g DBAO, 0.2 mL H_2O, 30 mg Sweetzyme and 3.3 mg $MgSO_4 \cdot 7H_2O$.

Increasing the temperature to 70 °C resulted in a faster formation of fructose. In addition, the equilibrium was shifted towards fructose which resulted in a maximum yield of 56 % after 4 hours. The formation of mannose was also increased to 5 % after 24 hours and up to 7 % after 72 hours. The yield of 56 % of fructose was still in the same range as would be expected in a water solution at the same temperature, and hence no thermodynamical advantage could thus far be detected with the DBAO/H_2O-system.

An additional temperature increase to 80 °C resulted in a reach of 59 % of fructose yield already after 4 hours. The formation of mannose via the Lobry de Bruyn-van Ekenstein transformation was further accentuated and after 24 hours as much as 11 % had been formed. At this point the fructose amount was unchanged and the formation of mannose was at the expense of glucose. A pH test of the IL/water-system revealed that the conditions were neutral. It was thus reasonable to believe that the Lobry de Bruyn-van Ekenstein transformation was enabled by specific base catalysis through the octanoate ion, i.e. independent of

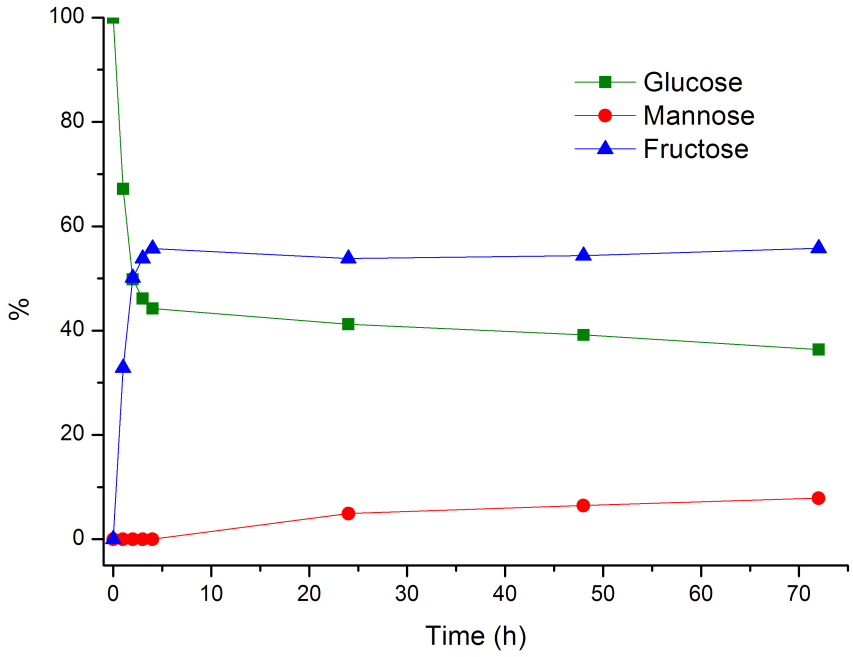


Figure 2.8. Enzymatic conversion of glucose to fructose in DBAO at 70 °C. Reaction conditions: 100 mg glucose, 0.8 g DBAO, 0.2 mL H_2O, 30 mg Sweetzyme and 3.3 mg $MgSO_4 \cdot 7H_2O$.

the concentration of hydroxide ions.

Control experiments in water were made for all three temperatures to validate that the batch of Sweetzyme exhibited a higher efficiency in water. The initial rates of fructose formation were 2-3 times faster in water confirming that isomerization rate for GI was retarded in the presence of DBAO. The calculated initial rate constants are shown in Table 2.4.

Table 2.4: Initial rate constants for glucose conversion with Sweetzyme.

Entry	T (°C)	Rate const. DBAO (h^{-1})	Rate const. H_2O (h^{-1})
1	60	0.27	0.71
2	70	0.35	1.14
3	80	0.80	1.46

Since the natural substrate of GI is xylose and its natural reaction the isomerization of xylose to xylulose, an investigation of the the DBAO/H_2O-system for this reaction was also made. The thermodynamics for xylose isomerization

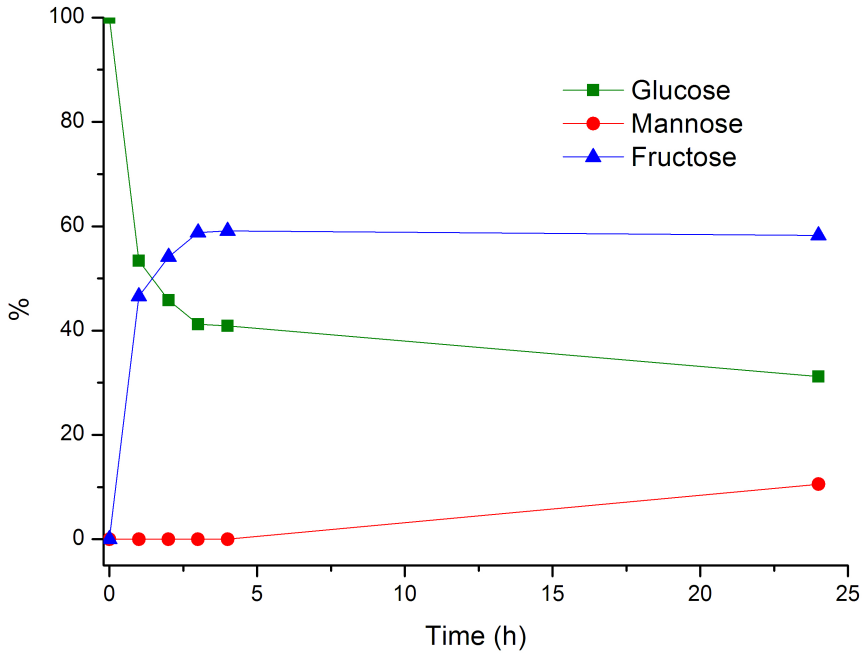


Figure 2.9. Enzymatic conversion of glucose to fructose in DBAO at 80 °C. Reaction conditions: 100 mg glucose, 0.8 g DBAO, 0.2 mL H_2O, 30 mg Sweetzyme and 3.3 mg $MgSO_4 \cdot 7H_2O$.

yield a different product distribution at equilibrium compared to glucose isomerization and the ratio of xylose and xylulose is 86:14.[83–85] The isomerization of xylose shown in Figure 2.10 was carried out at 60 °C and as expected a faster reach of equilibrium could be seen compared to the corresponding reaction for glucose. After 2 hours a product distribution of 86:14 between xylose and xylulose was reached. This ratio remained stable for 4 hours, but after 24 hours several different peaks appeared in the HPLC chromatogram indicating degradation of the sugars. This was not observed under the same conditions for glucose, which could be explained by the pentoses being more sensitive to degradation in the IL environment.

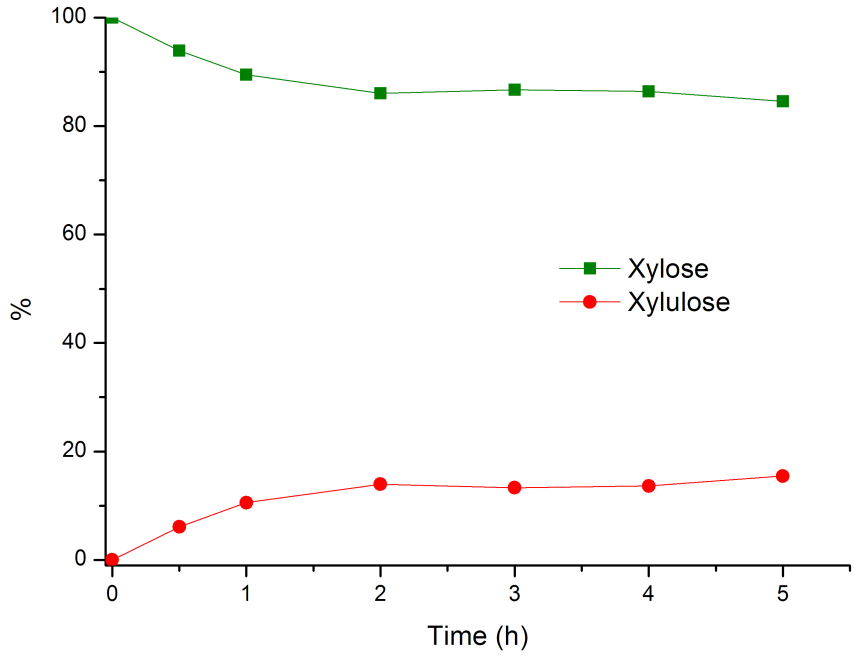


Figure 2.10. Enzymatic conversion of xylose to xylulose in DBAO at 60 °C. Reaction conditions: 100 mg xylose, 0.8 g DBAO, 0.2 mL H_2O, 30 mg Sweetzyme and 3.3 mg $MgSO_4 \cdot 7H_2O$.

2.4 Conclusions

The scarce literature on GI in alternative solvents implies that the activity of the enzyme is particularly sensitive to non-aqueous conditions. In the case of [EMIm]Cl and [BMIm]Cl, the chloride ions might disrupt the hydrogen bonding between the sugar and the magnesium ions in the active site, preventing isomerization. It should also be pointed out that the attempts with these ILs in the temperature range 60-80 °C are close to their melting point, why the solutions obtained were very viscous resulting in poor mass transfer between immobilized enzyme and sugar. The main incentive for finding an IL that could work as a solvent for the enzymatic isomerization of glucose to fructose, was the possibility to react fructose further to HMF. The results above and the dehydration attempts in DBAO described in the next chapter showed that an integration of an enzymatic reaction and subsequent dehydration would be very hard to achieve. The first dilemma with the enzyme catalyzed isomerization is that the solubility for

carbohydrates is limited. As much as 18 wt% of water was required to dissolve 10 wt% of glucose. This concentraion limits the possibility of making the process economical and also gives it little advantage over an integrated process under aqueous conditions.[86] Another possibility that is blocked using the DBAO/H_2O-system is using polysaccharides as starting material. The solubility of cellulose and starch was not quantified, but attempts to dissolve them in DBAO/H_2O gave clear indications that the solubility was limited.

An overall conclusion is that the properties of ILs favoring the dissolution of carbohydrates by disrupting the hydrogen bonding network are detrimental to the stability of GI. The discovery of an IL system for glucose isomerization should in spite of the points above not be dismissed. GI has proven to be particularly difficult in solvents other than pure water. The finding that ammonium carboxylates are particularly benign for enzyme activity might therefore provide important clues to understand the interaction of GI and solvent.

2.5 Experimental

All chemicals were used as received. D-glucose (99.5 %) and xylose (99 %) were purchased from Aldrich. D-fructose (puriss) was purchased from Riedel-de Haën. [EMIm]Cl and [BMIm]Cl were obtained from BASF while all other ILs were purchased from CLEA Technologies. All experiments were performed using a Radley Carousel 12 Plus Basic System with temperature control (±1 °C). Samples were analyzed by HPLC (Agilent 1200 series, Phenomenex Rezex RCM-Monosaccharide Ca^{2+} (%), 300 x 7.8 mm pre-packed column, MilliQ water as mobile phase, 80 °C, 0.6 mL/min). Peaks were identified from standards of all products and substrates.

2.5.1 General procedure for isomerization

Ionic liquid (0.8-1.0 g), $MgSO_4 \cdot 7H_2O$ (3.3 mg, 0.0135 mmol), water (0-0.2 mL, 0-18 wt%) and sugar (100 mg, 9 wt%) were stirred for 5 minutes and a clear homogeneous solution was obtained. Sweetzyme (30 mg) was added and the reaction was allowed to stir at 60-80 °C for a maximum of 72 hours. Samples were taken out during the reaction and analyzed by HPLC.

Synthesis of 5-(Hydroxymethyl)furfural in Ionic Liquids

3.1 Introduction

HMF is considered to be one of the most important platform chemicals in a world beyond cheap oil.[1,5] The challenge in making it with an economical and sustainable process is to find catalytic systems that can efficiently transform abundant non-edible biomass into HMF.

The past decade has shown a significant increase in research articles concerning HMF as a consequence of increased attention for chemicals from renewables. Since the early 1990s a steady increase of publications regarding HMF can be found in the literature as illustrated in Figure 3.11. In particular, the discovery of ionic liquids to be an efficient media for the conversion of hexoses to HMF has had a major impact on the increasing number of publications in the field.[42,43]

3.2 Mechanism of HMF formation

As mentioned in the first chapter, the formation of HMF is formed from the triple dehydration of fructose and the direct synthesis of HMF from glucose proceeds via the isomerization of glucose to fructose.[87–90] The enzymatic isomerization is enabled by a hydride-shift from C2 to C1 in glucose,[77] while the base catalyzed isomerization proceeds via an ene-diol mechanism.[82] Both should be considered

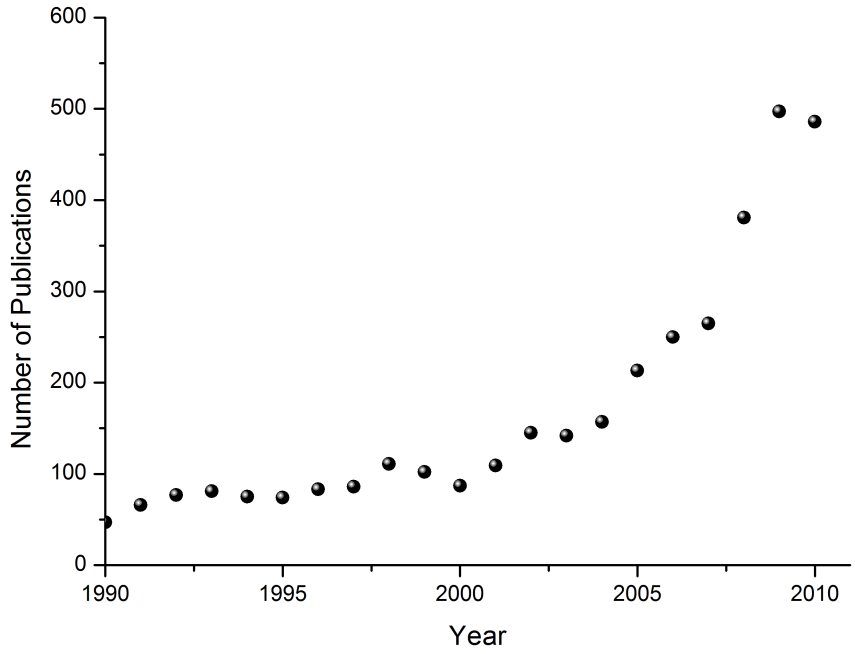
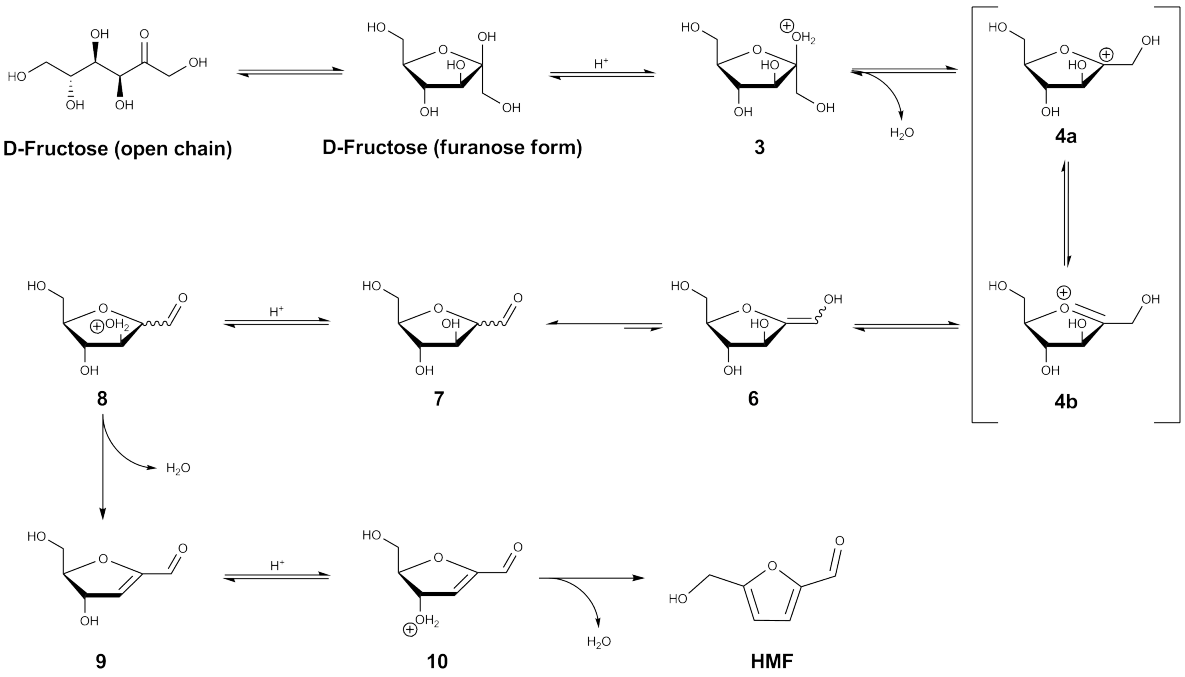


Figure 3.11. The number publications of HMF the years 1990-2010

as possible pathways when studying the mechanism for glucose dehydration.

The mechanism of fructose dehydration to HMF has been studied by several groups during the 20th century. Roughly, the debate concerning the mechanism divided chemists into two groups, those in favor of an open chain mechanism[91–95] and those advocating a mechanism involving only cyclic species.[20,21,26,40,96] An extensive study by Antal et al.[26] put forward substantial evidence for the cyclic route which is currently considered to be most likely pathway for HMF formation. The mechanism is drawn in Scheme 3.7 and has recently been strengthened by the observation of intermediate **9** by ^{1}H and ^{13}C NMR.[40]

Since the dehydration of glucose to HMF is in fact a combination of isomerization of glucose to fructose followed by a dehydration of fructose, the catalysts used for glucose dehydration must at least promote the former. The metal catalyzed mechanism in ILs has been discussed in a few papers regarding chromium,[62,88,97] tin[87] and germanium.[90] A computational study of the chromium(II) catalyzed isomerization in [EMIm]Cl concluded that the mechanism proceeded via a binuclear pathway where the mechanism was assumed to be the hydride-shift mechanism.[88] An NMR study has recently confirmed the hydride-shift as the mecha-



Scheme 3.7. The mechanism of HMF formation from fructose.[26,40]

nism for chromium catalyzed glucose dehydrations.[97]

Another interesting aspect of hexose dehydration in the presence of salts is the nature of the cation and anion. The halide ion was proven to be essential in the works of Binder and Raines,[64] where DMA and alkaline halide mixtures were investigated. The study demonstrated a linear relationship between the halide concentration and yield of HMF. Additionally, calculations have shown that [BMIm]Cl stabilizes the intermediates of the fructose dehydration, suggesting that the structure of the cation is also of importance.[98]

3.3 Chromium Catalyzed Synthesis of HMF

In our search for efficient conversions of glucose to HMF we decided to further investigate the chromium catalyzed systems in ILs. This was made in the light of the findings of the group of Zhang[62] and the work presented here was made parallel to later publications on chromium catalyzed systems.[63,64,88,97,99] Many of the conclusions drawn in those reports were also found in our research.

The study of chromium catalyzed systems was initiated by a screening of chromium(III) chloride in various ILs. A summary of the results is shown in Ta-

ble 3.5. The most important conclusion from this study was that ionic liquids containing halides were required to get reasonable conversion to HMF. Only one non-halogenic ionic liquid, 1-ethyl-3-methylimidazolium 2(2-methoxyethoxy)ethylsulfate ([EMIm][MEESU]) (entry 6), resulted in an HMF yield above five percent and only three more, [EMIm][$EtOSO_3$], choline dimethylphosphate ([Choline][dmp]) and 1,2,4-trimethylpyrazolium methylsulfate ([MMMPz][$MeOSO_3$]) resulted in conversion to HMF (entries 5, 7 and 8). In these three cases, a base (*t*-BuOK) was also added in catalytic amount. It is most likely that a simple base catalyzed isomerization of glucose to fructose occurred, after which the fructose was converted to HMF. The effect of the addition of base was otherwise inconclusive; in some experiments it appeared to slightly enhance yields (entry 1), but since this was hard to reproduce, it was concluded that it had no real significance.

The choice of halide as anion in the ionic liquids was also of significant impor-

Table 3.5: Dehydration of glucose in various ionic liquids with $CrCl_3 \cdot 6H_2O$ as catalyst[a]

Entry	Ionic Liquid	Time (h:min)	Temp. (°C)	Yield (mol %)	Selectivity (mol %)
1	[EMIm]Cl[b]	07:00	100	70.1	71.0
2	[EMIm]Cl	07:00	100	63.6	67.1
3	[MIm]Cl[b]	07:00	100	6.0	7.9
4	[MIm]Cl	07:00	100	6.1	8.4
5	[EMIm][$EtOSO_3$][b]	07:00	100	4.3	4.4
6	[EMIm][MEESU][b]	07:00	100	6.9	9.5
7	[Choline][dmp][b]	07:00	100	2.0	4.5
8	[MMMPz][$MeOSO_3$][b]	07:00	100	3.5	3.6
9	[BMIm]Cl[b]	07:00	100	64.9	66.4
10	[BMIm]Cl	07:00	100	68.1	69.3

[a] Reaction conditions: 1.0 g ionic liquid, 100 mg (0.56 mmol) glucose, 10 mol % catalyst [b] additional 10 mol % *t*-BuOK

tance. Yields of HMF dropped from about 70 percent using chloride or bromide as anion, to 20 percent using iodide as anion for the 1-ethyl-3-methylimidazolium cation (Figure 3.12). In between the two was 1-butyl-3-methylimidazolium bromide ([BMIm]Br), which resulted in about 50 % yield of HMF. This might be a result of ion-pairing effect between halide and imidazolium ring. Since the halide

is important in the mechanism of dehydration,[64] its interaction with the cation strongly affects the reactivity. This could be explained by interactions between hard and soft ions. The large imidazolium cation would most likely bind harder to the large iodide ion in a soft-soft interaction. Consequently, the dehydration gives the lowest yields using an iodide based ionic liquid. Chloride and bromide on the other hand, have a weaker interaction with the cation since they are harder due to their smaller ionic radius and therefore become more reactive, resulting in higher yields of HMF.

The alkyl chain also had influence on the reactivity. The best performance for the chromium catalyzed system was in [EMIm]Cl followed by [BMIm]Cl. Other groups have reported yields using [BMIm]Cl which were equivalent to ours for [EMIm]Cl.[64,63,100] Methylimidazolium chloride ([MIm]Cl), which have shown excellent results in the dehydration of fructose[101] only gave a yield of six percent.

The choice of chromium chloride also proved to be of some importance, even though not as significant as the factors mentioned above. Starting with anhydrous chromium(III) chloride generally resulted in slightly lower yields than starting with the hexahydrate. This could be explained by a better solubility for the hexahydrate complex than for the anhydrous one, which have later been confirmed by Zhang et al.[102]

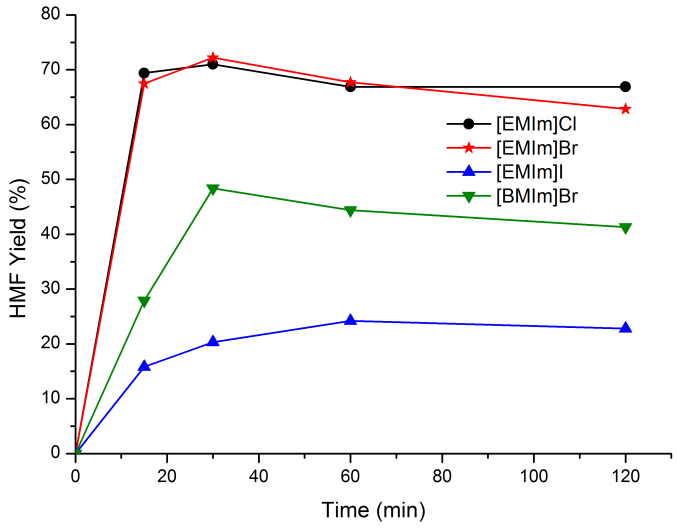


Figure 3.12. Dehydration of glucose at 120 °C as a function of time. General reaction conditions: 1.0 g ionic liquid, 100 mg (0.56 mmol) glucose and 14.8 mg (0.056 mmol) $CrCl_3 \cdot (H_2O)_6$.

3.4 Lanthanide Catalyzed Synthesis of HMF

The investigation for new catalysts continued with lanthanide chlorides which had been reported to have a catalytic effect on the dehydration of glucose to HMF in supercritical water.[103–105] For these experiments [EMIm]Cl and [BMIm]Cl were chosen due to superior performance in the previous section. The lanthanide halides chosen were $CeCl_3$, $PrCl_3$, $NdCl_3$, $DyCl_3$, $YbCl_3$ along with the pseudo halide $Yb(OTf)_3$ which is the strongest Lewis acid in the series. The initial results are shown in Figure 3.13 and Figure 3.14.

The lanthanides had an apparent effect on the dehydration of glucose to HMF, even though with much lower yields than for chromium. Interestingly, the two ILs exhibited a different pattern concerning the atomic number of the lanthanides. For [EMIm]Cl (Figure 3.13) the yield was very low for cerium and then increased to 13 % with promethium, after which it declined with atomic number. For [BMIm]Cl (Figure 3.14) the yield for cerium was also very low, but the yield then continuously increased from left to right in the period ending with the highest yield of 25 % for $Yb(OTf)_3$.

Another noteworthy difference between the ILs was the effect of catalyst

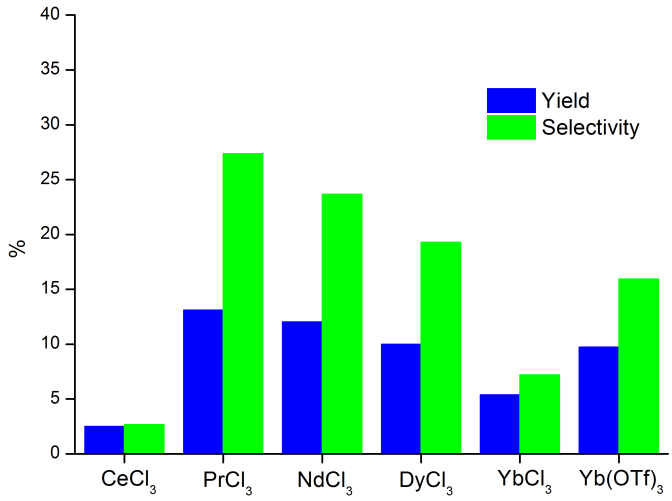


Figure 3.13. Lanthanide catalyzed dehydration of glucose in [EMIm]Cl. Reaction conditions: 1.0 g ionic liquid, 100 mg (0.56 mmol) glucose, 0.056 mmol catalyst, 140° C, 6 hours.

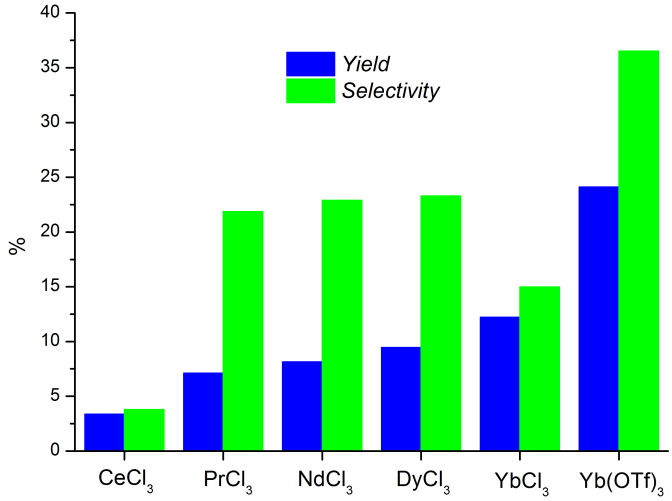


Figure 3.14. Lanthanide catalyzed dehydration of glucose in [BMIm]Cl. Reaction conditions: 1.0 g ionic liquid, 100 mg (0.56 mmol) glucose, 0.056 mmol catalyst, 140° C, 6 hours.

load. Increasing the loading of $YbCl_3$ from 10 to 30 mol percent had no effect for [EMIm]Cl whereas it had a high relative effect for [BMIm]Cl. These two phenomena accentuated the importance of the choice of IL for the dehydration

of HMF. The results are shown in Figure 3.15.

Since [BMIm]Cl appeared to be superior to [EMIm]Cl for the ytterbium

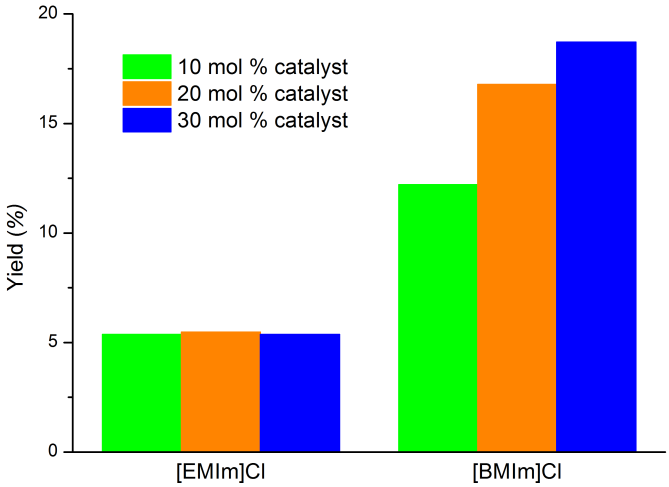


Figure 3.15. Dehydration of glucose in [EMIm]Cl and [BMIm]Cl at 140 °C for 6 hours with different amount of $YbCl_3$ catalyst. The reaction contained 1.0 g ionic liquid, 100 mg (0.56 mmol) glucose and 16 mg (0.056 mmol), 32 mg (0.112 mmol) and 48 mg (0.168 mmol) $YbCl_3$, respectively.

catalyzed dehydration, it was pursued further. In Figure 3.16 the yield and selectivity for the $YbCl_3$ catalyzed dehydration of glucose in [BMIm]Cl is shown. The best selectivity was reached already after ten minutes followed by an optimum yield after 30 minutes, after which it was degraded to humins.

When increasing the temperature to 200 °C the yield could be pushed slightly higher, but resulting in a very fast degradation of HMF. As can be seen in Figure 3.17 the optimum yield of 26 % was reached already after five minutes after which sharp decline in yield was noted.

The large difference in yield for the $YbCl_3$ catalyzed dehydration of glucose to HMF led to the idea that the longer alkyl chain of [BMIm]Cl was of some importance. As has been reported by the group of Welton [106,107] the alkyl chain length of the imidazolium cation has an impact of the reactivity of the counter ion. More hydrophobic imidazolium cations result in weaker ion-pairing between cation and anion and consequently the anion, in this case the chloride,

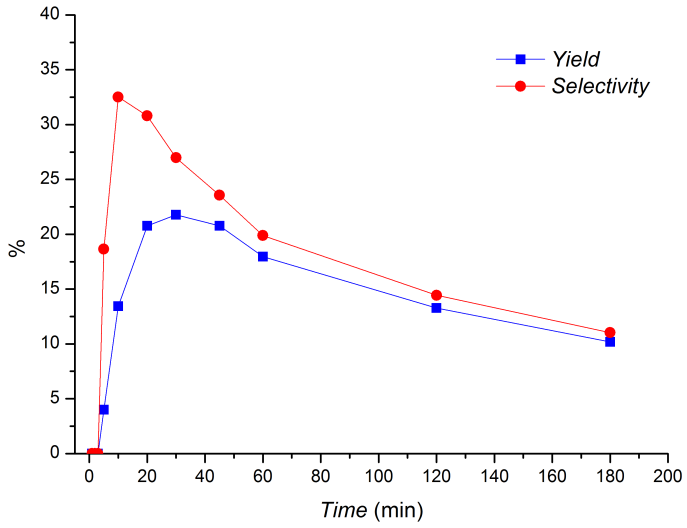


Figure 3.16. Dehydration of glucose in [BMIm]Cl catalyzed by $YbCl_3$ at 160 °C as a function of the reaction time. The reaction contained 1.0 g ionic liquid, 100 mg (0.56 mmol) glucose and 16 mg (0.056 mmol) $YbCl_3$.

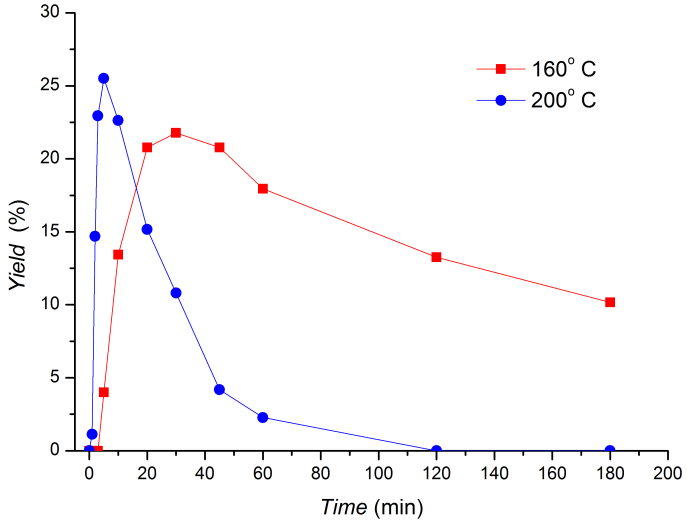


Figure 3.17. Dehydration of glucose in [BMIm]Cl catalyzed by $YbCl_3$ at 160 °C and 200 °C as a function of time. Both reactions contained 1.0 g ionic liquid, 100 mg (0.56 mmol) glucose and 16 mg (0.056 mmol) $YbCl_3$.

becomes more reactive. Since the chloride ion has an obvious effect on the reaction, increasing the alkyl chain length of the imidazolium cation might have an effect on the reaction. This can also be seen as a parallel to the hard and

soft theory discussed in the previous section when discussing the ionic radius. A larger ionic radius of the cation would hence make it softer and interact more poorly with the chloride ion. Two more alkyl imidazaolium chlorides, 1-hexyl-3-methylimidazolium chloride ([HMIm]Cl) and 1-octyl-3-methylimidazolium chloride ([OMIm]Cl), were tested for the reaction and the results in comparison with [EMIm]Cl and [BMIm]Cl are shown in Figure 3.18.

The yield increased with the increased chain length of the imidazolium

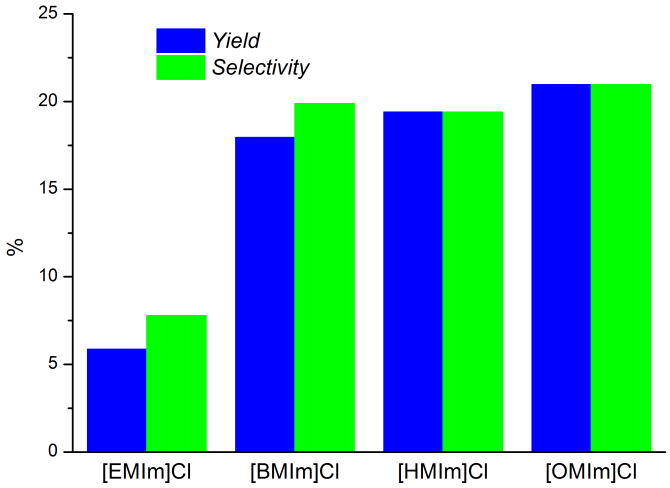
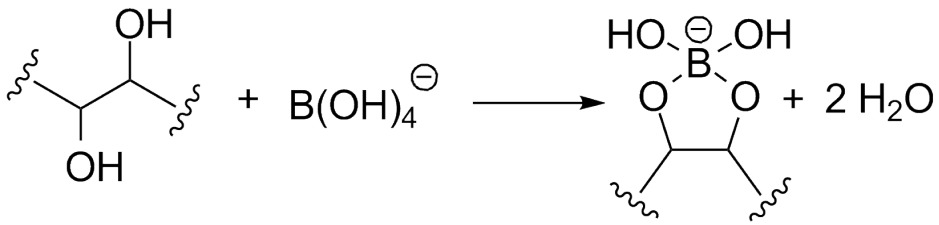


Figure 3.18. Dehydration of glucose in [EMIm]Cl, [BMIm]Cl, [HMIm]Cl and [OMIm]Cl at 160 °C for 1 hour. All reactions contained 1.0 g ionic liquid, 100 mg (0.56 mmol) glucose and 16 mg (0.056 mmol) $YbCl_3$.

cation, even though the increase from [BMIm]Cl to [OMIm]Cl was not as significant as from [EMIm]Cl to [BMIm]Cl. Nonetheless, the results indicated that the chromium catalyzed dehydration of glucose differs mechanistically from the ytterbium catalyzed dehydration. The difference between the two could be explained by the formation of different complexes in solution. The chromium dimer formed in the chromium catalyzed dehydration could simply diminish the influence of the ion-pairing between cation and anion making the hydrophobicity of the imidazolium cation less pronounced.

3.5 Boric Acid Catalyzed Synthesis of HMF

So far all described glucose dehydrations have been based on metal catalysts. A potential alternative was boric acid since it is well known that it forms complexes with sugars[108–110] (Scheme 3.8) as well as catalyzes glucose-fructose isomerization under basic aqueous conditions.[111,112]



Scheme 3.8. Formation of boric acid-diol complex.

Accordingly, we chose to test the dehydration in ILs with boric acid as catalyst. One equivalent of boric acid appeared to promote glucose dehydration and as with the chromium catalyzed reaction, [EMIm]Cl gave the best yields.

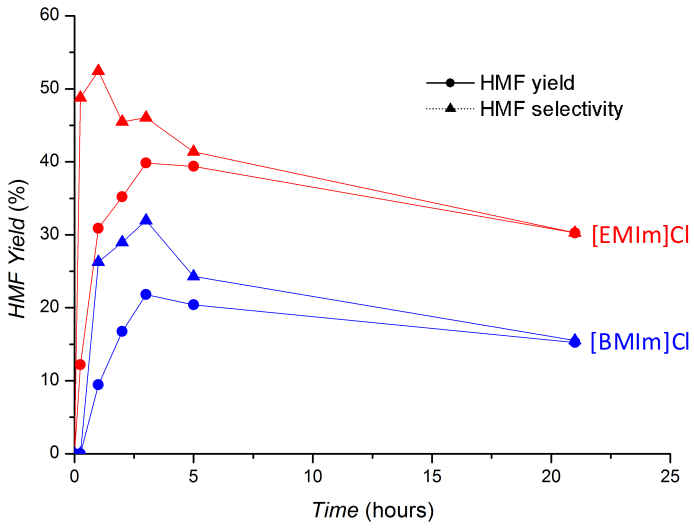


Figure 3.19. Dehydration of glucose in [EMIm]Cl at 120 °C. The reaction contained 1.0 g ionic liquid, 100 mg (0.56 mmol) glucose and 34.3 mg (0.56 mmol) boric acid.

The effect of boric acid in [EMIm]Cl was studied further with respect to boric acid ratio. The amount of boric acid was investigated in the range of 0-2.0 equivalents. As can be seen in Figure 3.20 the yield of HMF increased sharply up to 1.0 equivalent where it reached a short plateau and then declined slowly.

The obvious investigation after glucose dehydration with boric acid was to

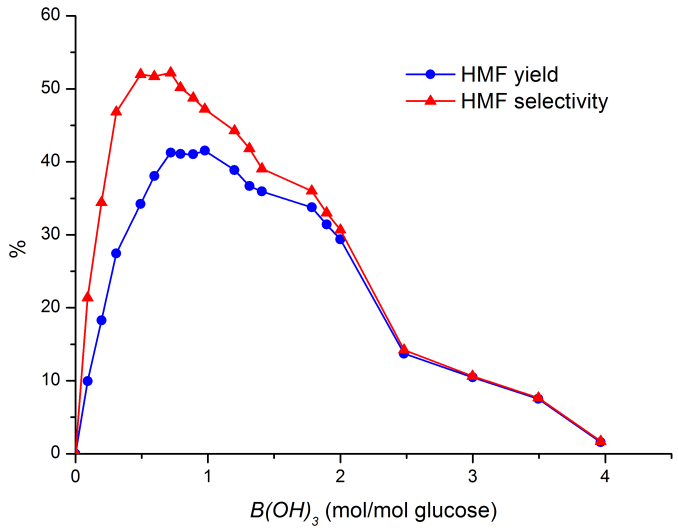


Figure 3.20. Dehydration of glucose in [EMIm]Cl at 120 °C with different concentrations of boric acid (1.0 g ionic liquid, 100 mg (0.56 mmol) glucose and boric acid (0-2.24 mmol)).

verify that boric acid promoted only glucose isomerization and did not affect fructose dehydration. As can be seen from Figure 3.21, boric acid had in fact a strong inhibitory effect on HMF yield. This led to the conclusion that boric acid only promoted the isomerization of glucose to fructose and that the subsequent dehydration of fructose to HMF was facilitated by [EMIm]Cl.

To complete the experimental study with boric acid as promoter dehydrations with feedstocks that have realistic potential for large scale synthesis of HMF were conducted. Starch, cellulose and sucrose were chosen for the experiments and are, as mentioned in Chapter 1, all considered to be potential feedstocks for future biorefineries. Additionally, attempts with maltose were made, a glucose dimer that was chosen for comparison rather than as a potential large scale feedstock. The results from the dehydrations are shown in Figure 3.22. The highest

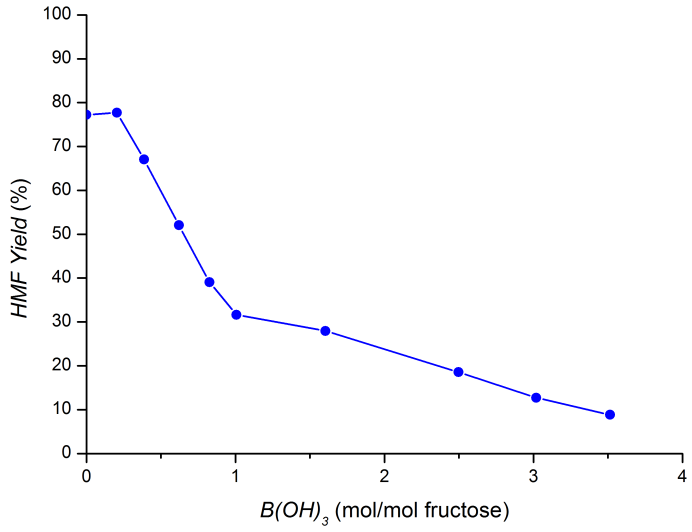


Figure 3.21. Dehydration of fructose in [EMIm]Cl at 120 °C with different concentrations of boric acid (1.0 g ionic liquid, 100 mg (0.56 mmol) fructose and boric acid (0-2.24 mmol)).

yield was obtained from sucrose which amounted to 66 %. This was higher than the combined yield of glucose and fructose. Both cellulose and starch gave a little more than 30 % yield, where starch interestingly reached maximum HMF yield later than cellulose. The HMF yield from maltose was surprisingly at the same level as both cellulose and starch suggesting that the degradation of HMF and intermediates was initiated before complete hydrolysis of the glycosidic bond, which explains the lower yield in comparison to free glucose.

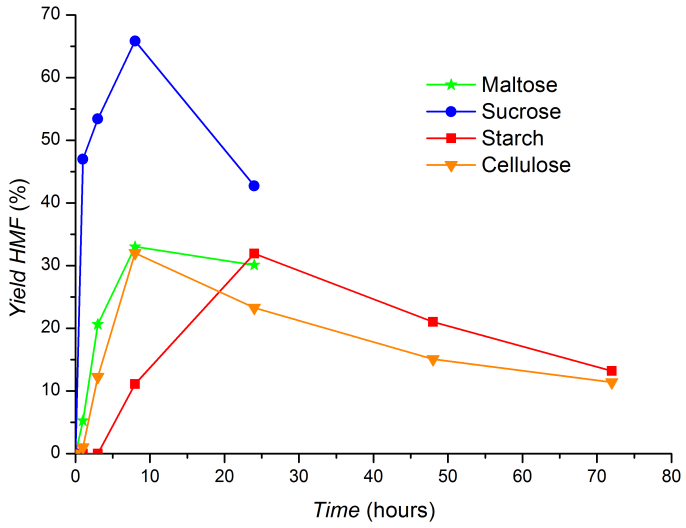


Figure 3.22. Dehydration of various carbohydrates in [EMIm]Cl at 120 °C with 0.5 equivalents of boric acid (1.0 g ionic liquid and 100 mg carbohydrate).

A smaller study using the high-boiling aprotic solvents DMA, DMSO, NMP and γ-butyrolactone together with LiCl or [EMIm]Cl as additives was also performed. The intention was to investigate if there was a positive solvent effect relative to pure [EMIm]Cl. In Figure 3.23 the results from using LiCl as additive are shown. Evidently, the yields were lower than for [EMIm]Cl and the best result was obtained in DMSO with a yield of 32 %. The yield for γ-butyrolactone was only half of that of DMSO, but the concentration of LiCl was lower since it did not dissolve 10 wt%. Second best was NMP with a slightly higher yield than DMA.

DMSO and NMP were investigated further using [EMIm]Cl as additive. The HMF yields were marginally improved up to 34 and 30 % for DMSO and NMP respectively (Figure 3.24). Clearly, the use of these solvents did not present any advantage and further studies in organic solvents were abandoned.

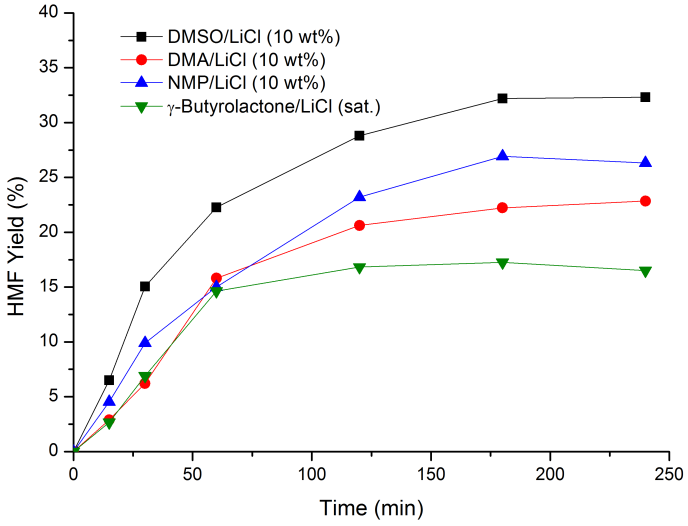


Figure 3.23. Dehydration of glucose in various solvents at 120 °C. The reaction contained 1.0 ml solvent, 10 wt% LiCl, 100 mg (0.56 mmol) glucose and 34.3 mg (0.56 mmol) boric acid.

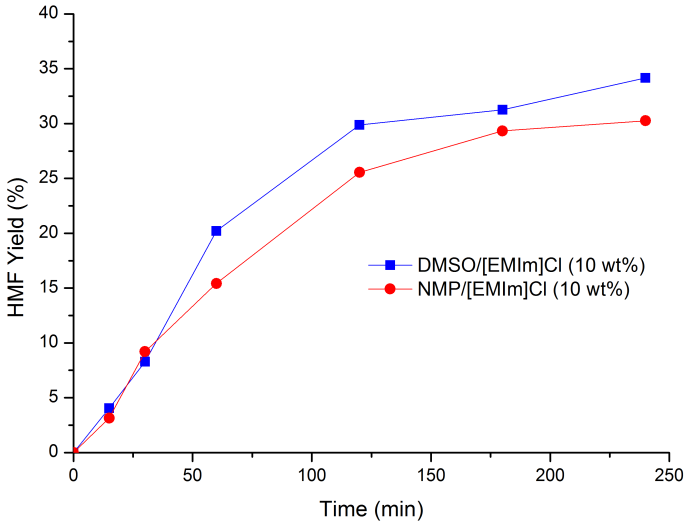


Figure 3.24. Dehydration of glucose in DMSO and NMP at 120 °C. The reaction contained 1.0 ml solvent, 10 wt% [EMIm]Cl, 100 mg (0.56 mmol) glucose and 34.3 mg (0.56 mmol) boric acid.

3.5.1 Computational Study of $B(OH)_3$-Sugar Complexes

In light of the above, a computational study of boric acid complexed with glucose and possible intermediates in the isomerization of fructose was performed. At

this point, both isomerization mechanisms mentioned in the previous section were taken into account and the transition states for both were calculated separately. The energies for the involved reaction intermediates can be seen in Figure 3.25.

The calculations showed clearly that complexation with one mole of boric

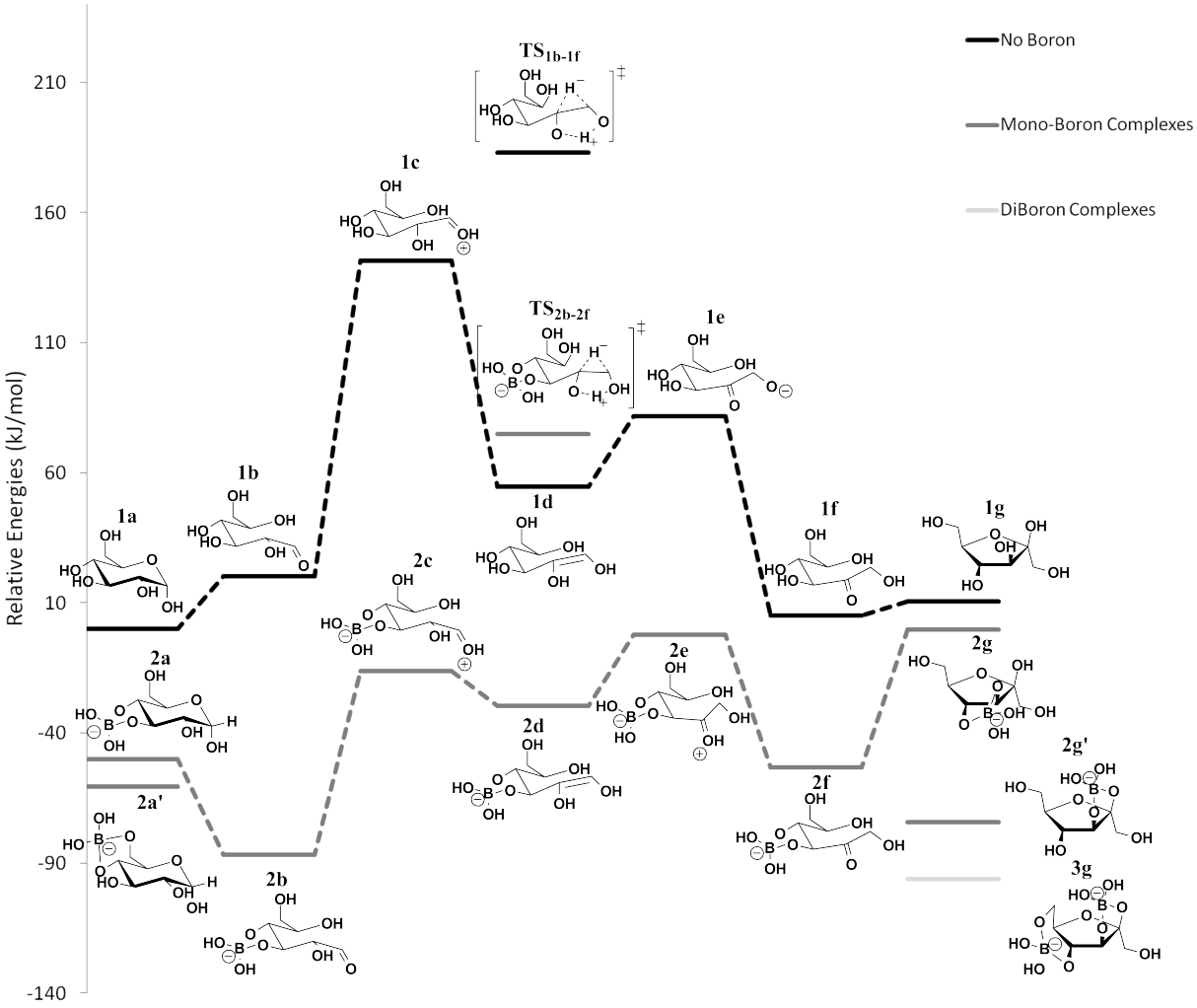
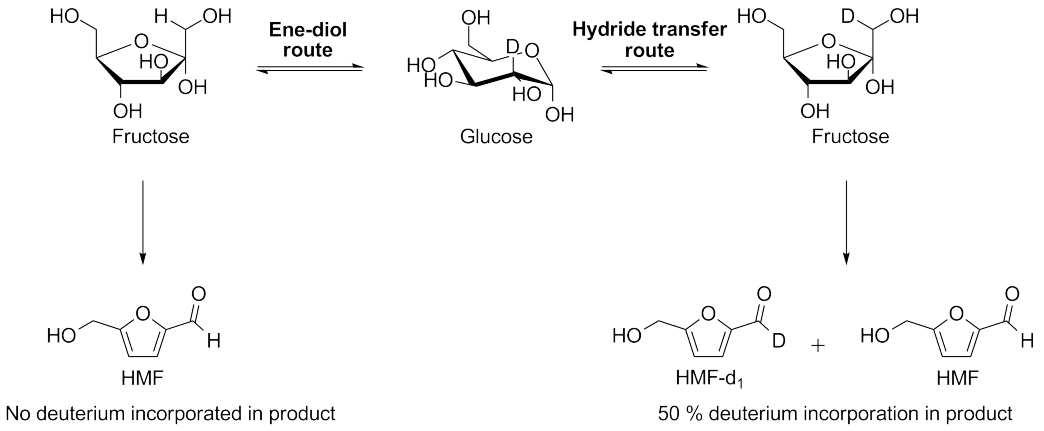


Figure 3.25. Overview of the two reaction pathways for isomerization of glucose to fructose. The stabilizing effect of boric acid coordination along the reaction pathway is clear.

acid dramatically decreased the activation energy for the transition from glucose to fructose. The pathway via the ene-diol mechanism had lower energy than the hydride shift mechanism. The energy for the initial complexes of glucose proved to be lowest for the 4,6-complex (**2a'**), but the 3,4-complex (**2a**) resulted in a lower energy for the overall mechanism to fructose. The 3,4-borofructose

(**2g**) formed at the end of the reaction had similar energy compared to unbound fructose, unlike the 2,3-borofructose (**2g'**) which was significantly more stable. This led us to believe that **2g** after complete isomerization lost its boric acid and was subsequently subject to either dehydration to HMF or complexed with boric acid to form the more stable **2g'**. Since the the C2-oxygen of **2g'** is blocked, this complex cannot undergo dehydration. However, it could be complexed further to the diboro-complex 2,3,4,6-diborofructose, which had an even lower energy compared to **2g'**. The explanation in the lower energies for these compounds lies in the fact that boric acid is bound *cis* to the sugar, whereas **2g** has boric acid bound *trans* and thus greater steric strain.

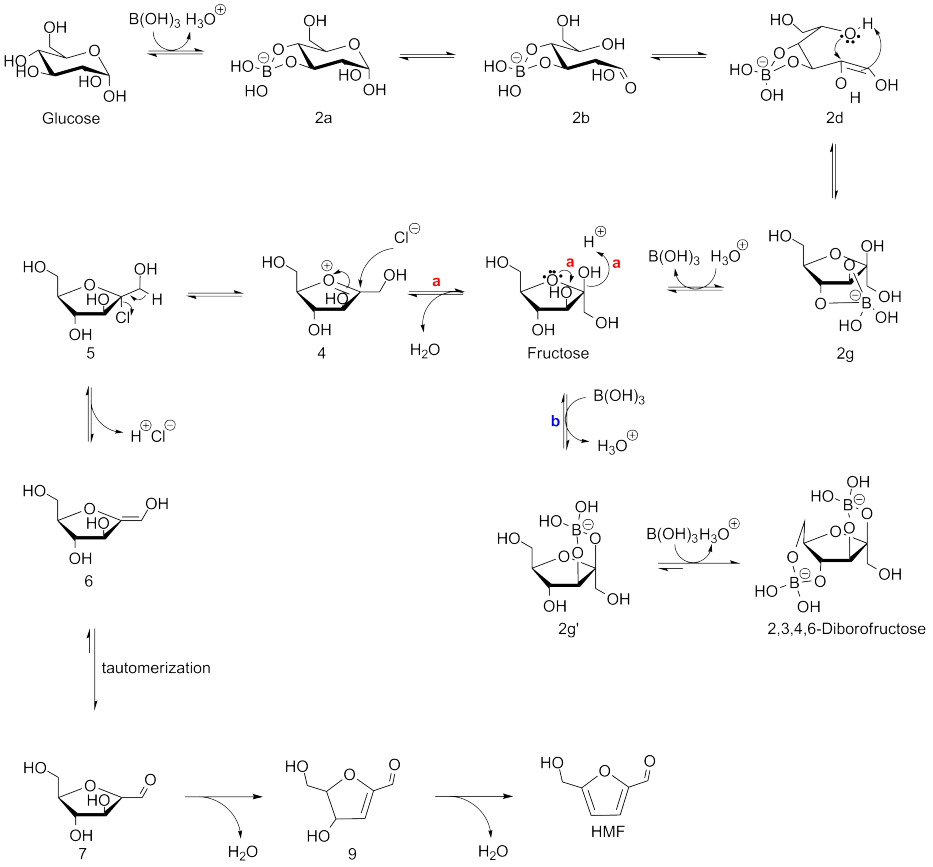
The lower energy for the ene-diol pathway was not sufficient evidence for establishing it as the true mechanism. As mentioned previously, the enzymatic isomerization proceeds via the hydride-shift mechanism[77] as well as the chromium catalyzed isomerization.[97] In order to rule out one of the mechanisms we reacted glucose-2-d_1 under the same reaction conditions as in the previous experiments. The outcome of a hydride-shift mechanism would be 50 % incorporation of the deuterium in the aldehyde proton of HMF in the final product, whereas an ene-diol mechanism would result in no deuterium incorporation at all. The two possible scenaria are depicted in Scheme 3.9.



Scheme 3.9. Theoretical amount of deuterium incorporated in HMF by the two possible isomerization mechanisms.

The product from the isotopic labeling studies was analyzed by ^{1}H NMR and

MS and concluded that less than a few percent of deuterium was incorporated (see Figure A7-A10 in Appendix). The pathway for the boric acid promoted isomerization in [EMIm]Cl was hence the ene-diol mechanism. From these new findings, together with the previously established mechanism for fructose dehydration (Scheme 3.7), an overall mechanism was derived shown in Scheme 3.10.



Scheme 3.10. Putative mechanism for the dehydration of glucose to HMF in imidazolium chlorides with boric acid as promoter.

3.6 Miscellaneous Catalysts

In addition to the catalysts mentioned above, a few more were tried. Germanium has also shown to have an effect on the isomerization of glucose to fructose[79] and GeO_2 was therefore tried as catalyst. There was no conversion using [BMIm]Cl as solvent, but [EMIm]Cl gave a yield of six percent after two hours. Since this was inferior to all the others tried, it was not pursued any further. It was later

reported that $GeCl_4$ can convert glucose to HMF in good yields in ILs.[90] Apparently, having a germanium ion in the presence of a large surplus of chloride ions was not sufficient to form the desired complex which promotes the isomerization. Tungsten has shown catalytic dehydration of fructose at low temperatures.[113] This urged an attempt to try a tungsten compound as catalyst for the dehydration of glucose using $H_3PO_4(WO_3)_{12}$. In opposite to GeO_2, conversion of glucose to HMF was only found in [BMIm]Cl, resulting in a yield of five percent. Identical experiments in [EMIm]Cl resulted in no HMF formation even though glucose was fully converted. Attempts were also made with $CoCl_2$ and $Co(acac)_2$ since these are interesting for a one-pot process from glucose to FDA. None of these showed any catalytic effect however, and were not investigated any further. Based on the results from dehydration with borate, a boric acid containing zeolite, B-ZSM-5(12) was tried as heterogeneous catalyst in [EMIm]Cl and [BMIm]Cl. A small catalytic effect was observed in [EMIm]Cl which afforded an HMF yield of 8 %, whereas no HMF formation was observed in [BMIm]Cl.

3.7 Fructose Dehydration in DBAO

Based on the results obtained in the previous chapter for glucose isomerization, the dehydration of fructose to HMF was investigated in DBAO. Unfortunately, no formation of the desired product was observed. Attempts using Lewis and Brønsted acid catalysts like WCl_6,[113] $CrCl_3$,[62,63] and HCl[98] were made in anhydrous DBAO, but only resulted in caramellization of the sugar. The combination of elevated temperature and acid catalysts caused a significant degradation of fructose which was not observed during the isomerization. The results stress once more the vital role of the anion for sugar dehydration. In addition, the alcohol functionality of the cation (dibutylethanolammonium) might interfere with the Lewis acid catalysts and hamper their complexation with the sugar.

3.8 Conclusions

Chromium(III) chloride was superior as catalyst for the direct conversion of glucose and its corresponding polymers to HMF in ILs. Only imidazolium based

ionic liquids with chloride as anion gave yields that have potential for large scale production of HMF. Among these ILs, [EMIm]Cl and [BMIm]Cl were superior in performance. Boric acid showed promising results even though the yields presented here did not match that of chromium.

The IL best suited for enzymatic isomerization of glucose to fructose, DBAO, was unfortunately unsuitable for HMF synthesis. Since sugar dehydration appears to require a halide present for efficient and selective conversion, it would be an arduous task to find an IL that fulfills those criteria and at the same time is benign to the enzyme. A conclusion thus far would therefore be that a one-pot reaction from glucose to HMF would has to be catalyzed by a metal chloride or boric acid in an alkylmethylimidazolium chloride IL.

Creating an efficient catalytic system would most likely benefit from having a dual function: one catalytic specie promoting isomerization and the other promoting dehydration. The chromium catalyst has the best performance since it promotes both isomerization and catalyzes the conversion of fructose to HMF.[102] This does not necessarily have to be achieved by one single catalyst as in the case of chromium, but could be a combination of an isomerization promoter such as boric acid together with an efficient dehydration catalyst. A continued screening with boric acid in combination with other lewis acid catalysts could result in dual functional catalytic systems that would be preferable to chromium both regarding selectivity and environmental impact. Further investigation of boric acid derivatives could also be envisioned, where several boronic acids are screened as catalysts for the dehydration reaction. If a boric acid derivative which forms a fructose complex with higher energy than **2g** and still promotes the isomerization of glucose could be found, it could result in a catalytic system which provides higher HMF yields.

3.9 Experimental

3.9.1 Materials and Equipment

All chemicals were used as received. D-glucose (99.5 %), D-glucose-2-d_1 (98 atom % D), dimethyl sulfoxide (98 %), cellulose (powder, ca 20 micron), tetramethylurea (99 %), γ-butyrolactone (98 %) and *N*-methyl-2-pyrrolidone (99 %) were purchased from Aldrich. Boric acid (puriss), starch (p.a.) and D-fructose (puriss) were purchased from Riedel-de Haën. Ethylene glycol (normapur) and D-maltose (p.a.) were purchased from Prolabo. Sucrose (99 %) was purchased from Alfa Aesar. [EMIm][$N(CN)_2$] (98 %), [Choline][dmp] (98 %) and [EMIm][$C_2H_5OSO_3$] (98 %) were purchased from Solvent Innovation, while all other ionic liquids were obtained from BASF (>95 %). The dehydration experiments were performed under nitrogen atmosphere using a Radley Carousel 12 Plus Basic System with temperature control (±1 °C). All samples were analyzed by HPLC (Agilent 1200 series, Bio-Rad Aminex HPX-87H, 300 mm x 7.8 mm pre-packed column, 0.005 M H_2SO_4 mobile phase, 60 °C, 0.6 mL/min). The HMF yields and selectivities were based on conversion of glucose and confirmed by calibration of standard solutions of the products and reactants involved.

3.9.2 General dehydration procedure

A 40 mL reaction tube was charged with ionic liquid (1 g) and boric acid (34.6 mg, 0.56 mmol) and heated at 100 °C for 1 hour. Glucose (100 mg, 0.56 mmol) or other carbohydrate (0.56 mmol) was then added and the solution stirred for 3 hours at 120 °C. After reaction the reaction tube was cooled in an ice bath and water (5 mL) added. The solids were filtered off and the filtrate analyzed by HPLC. Alternatively filtrate was extracted with ethyl acetate (3 x 30 mL) and the solvent then removed in vacuo.

3.9.3 Computational Method

Density functional theory (DFT) in combination with the B3LYP functional [114–116] as incorporated in Jaguar version 7.6 from Schrodinger Inc. [117] was used for the calculations. In the current study we employed the LACVP* basis set in Jaguar

which uses the Hay-Wadt small-core ECP and basis set for boron[118] and the 6-31G* basis set for the remaining elements. Solvation energies were obtained using the PB-SCRF solvation model[119,120] employing parameters suitable for dichloromethane (dielectric constant 9.08 and probe radius 2.33237 Å). In this model the solvent is described as a continuum, where the molecule is put into a reaction field consisting of surface charges on a solvent accessible surface constructed using a hypothetical spherical solvent probe molecule with the indicated radius.[121] The wave function and the reaction field charges are solved iteratively until self-consistency is reached. Physical data on ionic liquids in the literature are still scarce, for example it was not possible to find a dielectric constant for [EMIm]Cl. Thus, we have in the current study used parameters suitable for dichloromethane since its dielectric constant ($\epsilon = 7.26$) was close to the ones reported of several 1-ethyl-3-methylimidazolium based ionic liquids.[122,123]

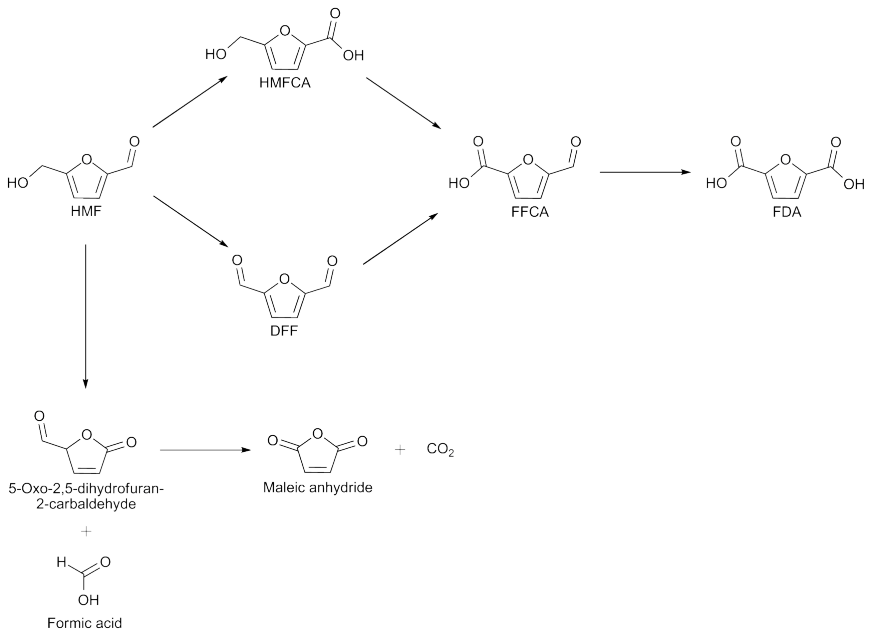
In previous projects[124,125] it was found that energies calculated with the continuum solvent model gives a fair correspondence with experimental ratios, but for a quantitative agreement we frequently also need to account for the vibrational component of the free energy. The free energy adjustment was then added to the corresponding energy determined in solvent, to arrive at a composite free energy that is our best estimate of the free energy in solvent.

Aerobic Oxidations in Ionic Liquids

4.1 Introduction

The oxidation of HMF to the corresponding diacid FDA is believed to be one of the most important derivatives of the furanic platform. As a replacement for terephtalic acid in PET it has an enormous potential in becoming a commodity chemical on a multi million ton scale. Polymers of FDA are not only limited to polyethylene derivatives. Synthesis of polyamides from FDA and aromatic diamines or benzidine give materials that exhibit very high thermal resistance.[12] Additionally, FDA and its derivatives have pharmaceutical applications. The diacid itself is a strong complexation agent for calcium, lead and copper ions and can be utilized for the removal of kidney stones.[126] The FDA diethyl ester has proven to be a strong anasthetic[127] and the dicalcium salt of FDA and FDA anilidines have shown anti-bacterial properties.[128,129]

The synthesis of FDA is facile using traditional stoichiometric reagents such as $KMnO_4$ affording nearly quantitative yields.[130] Another effective oxdiation method, albeit with lower selectivity, is the use of nitric acid.[131–133] Catalytic oxidations were first studied by the group of van Bekkum using molecular oxygen together with platinum and palladium catalysts.[134,135] Recently, the use of gold nanaoparticles has shown to be an effective catalyst both for the synthesis of FDA itself and for its methyl ester.[136–138] The oxidation of HMF proceeds via diformyl furfural (DFF) or 5-hydroxymethyl-2-furancarboxylic acid (HMFCA) to 5-formyl-2-furancarboxylic acid (FFCA) which is rapidly converted to FDA.[134] HMF can also be oxidized to DFF and maleic anhydride selectively using vanadium catalysts.[139–141] The different oxidation products of HMF are depicted in Scheme Scheme 4.11.



Scheme 4.11. Different oxidation products of HMF.

A major problem with the synthesis of FDA is its extremely low solubility in both water and organic solvents,[142] which makes its catalytic oxidation in water using heterogeneous catalyst require an equimolar amount of base to ensure that the product stays in solution. To circumvent this problem a heterogeneous catalytical aerobic oxidation in an IL could be envisioned. In such a process the catalyst would be filtered from the IL/FDA solution after complete reaction where after the product would be crystallized by the addition of water. The water would subsequently be removed from the mother liquid under reduced pressure and the IL recycled.

The growth of ILs as a research field has also brought about several studies on oxidations in ILs. These have primarily been conducted in 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIm][BF_4]) and 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIm][PF_6]). Since these ILs have proven to be sensitive to hydrolysis which leads to the release of HF[47,143] and subsequently has an impact on the reaction, we chose to omit these liquids from our study. Among the oxidations in ILs there are a large number of epoxidations of alkenes[144–148] as well as oxidations of alcohols to aldehydes or ketones[149–151]. An interesting example of the oxidative Glaser coupling in ILs can also be found.[152] These trans-

formations have used H_2O_2, NaOCl, Dess-Martin periodate, MnO_2 and *meta*-chloroperoxybenzoic acid (mCPBA) as oxygen donor. The use of dioxygen as bulk oxidant has also been demonstrated by several groups.[153–167] Of interest for our work is the oxidation of alcohols to ketones in quaternary ammonium salts over different homogeneous ruthenium catalysts.[153] The studied ruthenium catalysts had superior performance in tetramethyl ammonium hydroxide and *N*-Methyl-*N*,*N*-dioctyloctan-1-ammonium chloride (Aliquat 336) compared to [BMIm][BF_4] and [BMIm][PF_6].[154]

In our lab, the use of $Ru(OH)_x$ on various supports as catalysts for the oxidation of HMF and other alcohols was conducted, and thus we decided to test them for the use in ILs. These supported ruthenium hydroxides were introduced by Yamaguchi and co-workers[168] and have been proven to be excellent catalysts for aerobic oxidations. They have been widely employed for oxidations of alcohols[169] and oxygenation of primary amines to amides.[170] We found no literature on aerobic oxidations in ILs catalyzed with solid ruthenium hydroxide, which is most likely because there is seldom any obvious rational for a process based on such a system. In many reactions the desired product is easily separated by extraction or distillation, and hence does not benefit from an extra unit operation by filtering off a heterogeneous catalyst.

4.2 Oxidation of HMF in [EMIm]Cl

In the previous chapter it was shown that [EMIm]Cl and [BMIm]Cl were superior ILs for converting hexoses to HMF. The study of the ruthenium catalyzed oxidation in ILs was therefore initiated with a short survey using [EMIm]Cl as solvent. The oxidation attempts were made in open tubes at ambient pressure with nine different supports for the $Ru(OH)_x$-catalyst. The heterogeneous mixtures were reacted at 140 °C for 24 hours and the results are shown in Table 4.6.

In general, low yields for all oxidation products were obtained. Nevertheless, the results gave indications of which catalysts could be advantageous for further studies under different reaction conditions. Some reactions gave higher yield of HMFCA (entries 7-9) which showed promise for further studies. The different performance of the catalysts in [EMIm]Cl could be the cause of several

Table 4.6: HMF oxidation in [EMIm]Cl with various $Ru(OH)_x$/support as catalyst.[a]

		Conversion (%)	Yield (%)		
Entry	Catalyst	HMF	DFF	HMFCA	FDA
1	$Ru(OH)_x/TiO_2$	92	0	1	3
2	$Ru(OH)_x$/spinel	89	0	7	3
3	$Ru(OH)_x/Fe_2O_3$	99	0	14	5
4	$Ru(OH)_x/ZrO_2$	84	0	3	5
5	$Ru(OH)_x/CeO_2$	86	0	7	4
6	$Ru(OH)_x$/HAp	81	0	4	4
7	$Ru(OH)_x$/HT	>99	0	20	5
8	$Ru(OH)_x$/MgO	>99	0	20	2
9	$Ru(OH)_x/La_2O_3$	>99	0	25	1

[a] Reaction conditions: 1.0 g [EMIm]Cl, 68 mg (0.54 mmol) HMF, 100 mg catalyst (2.5 wt% Ru, 0.025 mmol), 140 °C, 24 hours, ambient air pressure.

reasons. The chemical interaction with the IL and the support can indirectly affect the catalytic performance, since the support possibly has an interaction with ruthenium and consequently hamper the oxidation of HMF. In addition, the interaction between IL and support can influence the viscosity of the reaction mixture which consequently affects mass transfer between dioxygen and catalyst.

4.3 Oxidation of HMF in Various Ionic Liquids

Since the IL can have a significant contribution to the reactivity of different catalyst supports, a more extensive study in several ILs together with six different catalysts was made. The solid ruthenium catalysts chosen were $Ru(OH)_x/CeO_2$, $Ru(OH)_x/La_2O_3$, $Ru(OH)_x$/HT, $Ru(OH)_x$/spinel and RuMnCe/CeO_2. Additionally, the catalyst precursor, $RuCl_3$, was chosen for comparison. $RuCl_3$ is a commonly employed oxidation catalyst in organic synthesis (the active specie being RuO_4) together with Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$), $NaIO_4$ and NaOCl.[171–173] The screening was performed by using the same procedure as for the initial study in [EMIm]Cl. The yield of the different oxidation products as a function of catalyst and IL are depicted in Figure 4.1-4.3.

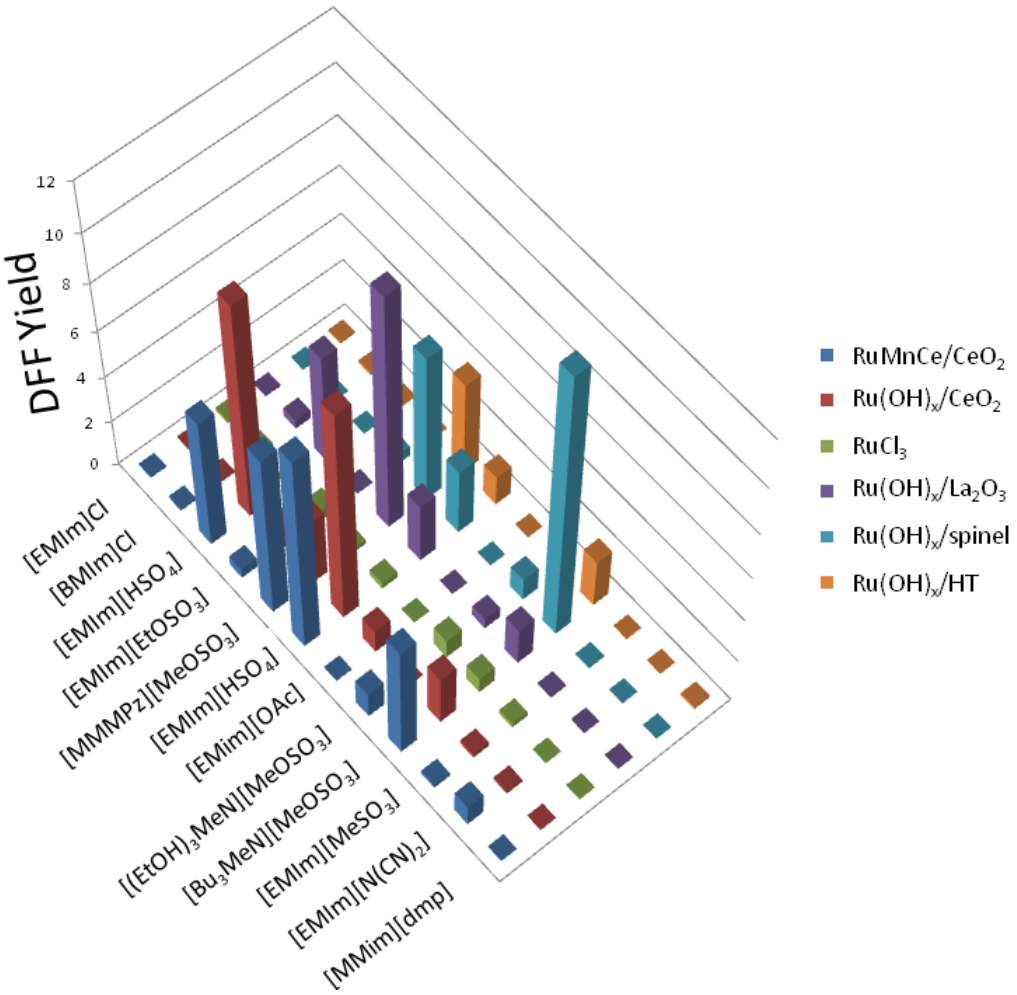


Figure 4.26. Yield of DFF with different catalysts in different ILs. Reaction conditions: 1.0 g IL, 68 mg (0.54 mmol) HMF, 100 mg catalyst (2.5 wt% Ru, 0.025 mmol), 140 °C, 24 hours, ambient air pressure.

The oxidation of the hydroxyl group of HMF yields DFF. In most ILs, e.g. [EMIm]Cl and [BMIm]Cl, no DFF was observed at all. However, in tributylmethylammonium methylsulfate ($[Bu_3MeN][MeOSO_3]$) with $Ru(OH)_x$/spinel as catalyst, a yield of 12 % was obtained. Also $[EMIm][HSO_4]$ together with $Ru(OH)_x/CeO_2$ and $[MMMPz][MeOSO_3]$ with $Ru(OH)_x/La_2O_3$ afforded yields around 10 %. The only catalyst that gave no DFF in any IL was the homogeneous precursor $RuCl_3$.

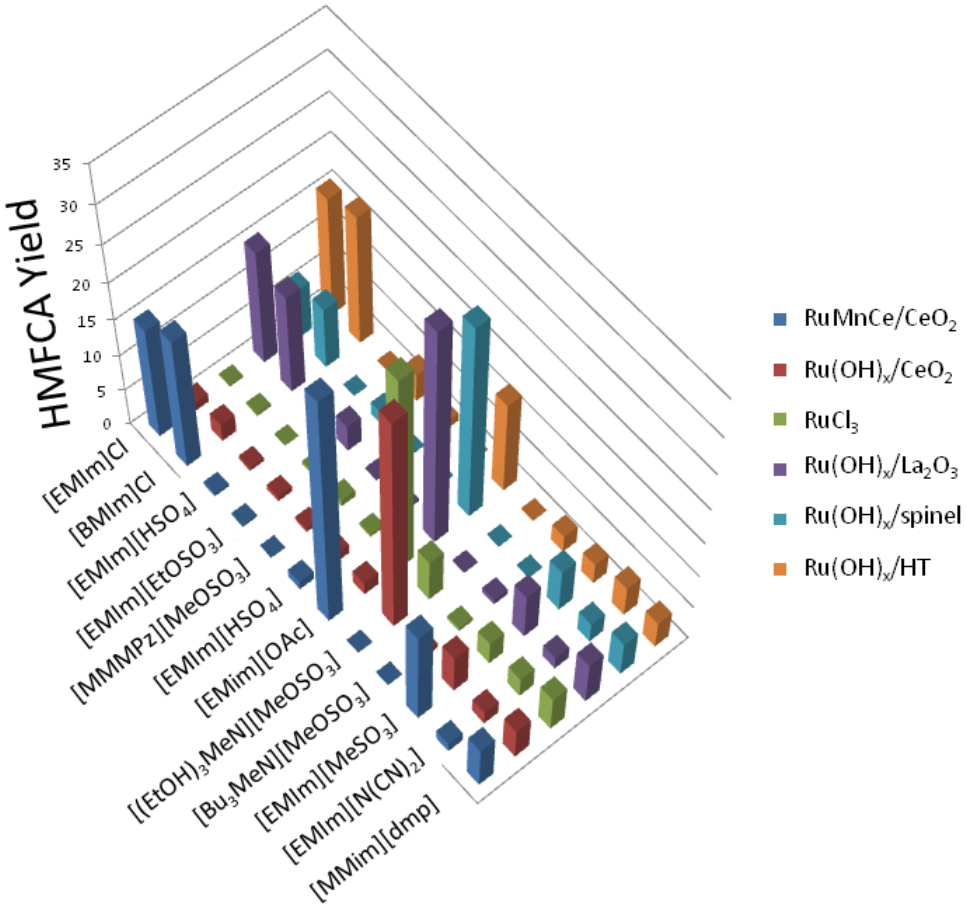


Figure 4.27. Yield of HMFCA with different catalysts in different ILs. Reaction conditions: 1.0 g IL, 68 mg (0.54 mmol) HMF, 100 mg catalyst (2.5 wt% Ru, 0.025 mmol), 140 °C, 24 hours, ambient air pressure.

An oxidation of the aldehyde group on HMF gives HMFCA which was formed to a much larger extent compared to the other two oxidation products. For [EMIm]Cl and [BMIm]Cl, yields between 15 and 18 % were obtained for $Ru(OH)_x/CeO_2$, $Ru(OH)_x/La_2O_3$ and $Ru(OH)_x$/HT. Most noteworthy were the results for [EMIm][OAc] which together with all catalysts except $Ru(OH)_x$/HT and $Ru(OH)_x/CeO_2$ afforded yields around 30 %. The yield of HMFCA using $RuCl_3$ was here comparable to the solid ruthenium catalysts.

The desired end product FDA was formed in very modest amounts in the screening. One exception was the reaction in [EMIm][HSO_4] using $Ru(OH)_x$/HT as catalyst which afforded a yield of 20 %. Surprisingly, no other ILs gave FDA with $Ru(OH)_x$/HT and no other catalysts gave FDA together with [EMIm][HSO_4]. For [EMIm][OAc] the same catalysts that resulted in fairly good HMFCA yields gave conversion to FDA with yields in the range of 5 to 13 %.

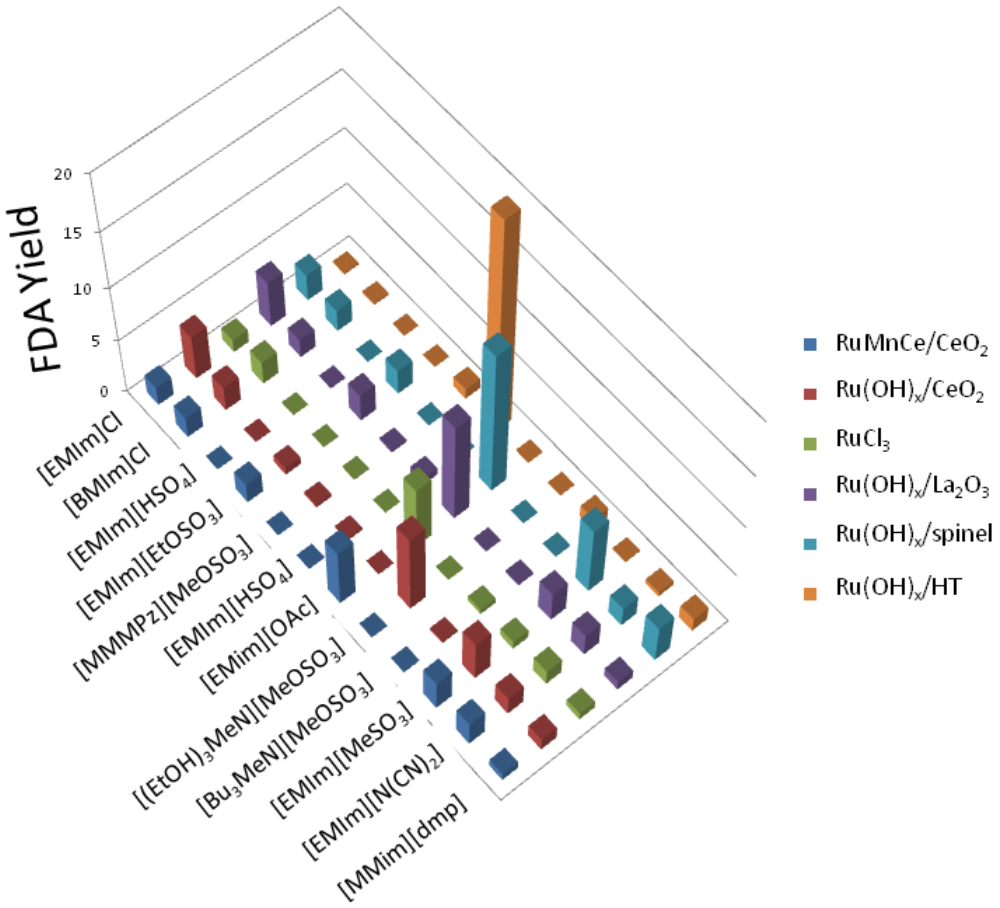


Figure 4.28. Yield of FDA with different catalysts in different ILs. Reaction conditions: 1.0 g IL, 68 mg (0.54 mmol) HMF, 100 mg catalyst (2.5 wt% Ru, 0.025 mmol), 140 °C, 24 hours, ambient air pressure.

4.4 Oxidation of HMF in [EMIm][OAc] at Ambient Pressure

The first screening above revealed [EMIm][OAc] as an IL with potential for aerobic oxidations. This could be explained by the lower viscosity of [EMIm][OAc] compared to many of the other ILs in the screening or by a higher solubility of dioxygen in the IL. In general the solubility of dioxygen in ILs is low compared to other gases like CO_2 and H_2.[174–178] A disadvantage with [EMIm][OAc] for this particular reaction is its detrimental effect on the stability of HMF.[179] To alleviate this effect a lower reaction temperature was chosen. The reaction progress was investigated over time and two catalysts were tested; $Ru(OH)_x$/spinel and $Ru(OH)_x/La_2O_3$.

In Figure 4.29 the oxidation using $Ru(OH)_x$/spinel in [EMIm][OAc] is shown.

The yield of HMFCA now amounted to 42 % after 28 hours, clearly indicating that lowering the reaction temperature had a major impact on yield. Even though the maximum yield was not reached until 28 hours, it was close to being reached already after 6 hours with 39 %.

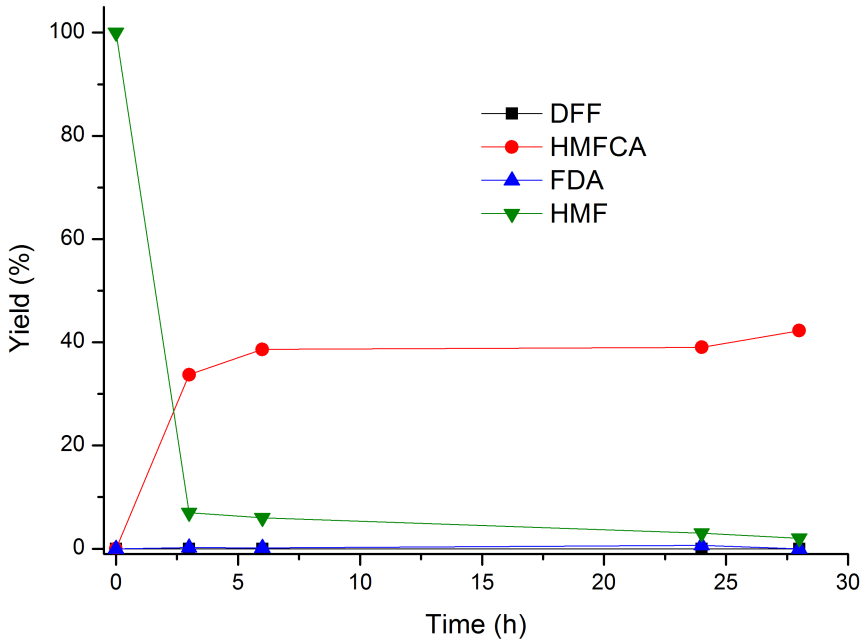


Figure 4.29. Oxidation of HMF with $Ru(OH)_x$/spinel in [EMIm][OAc] at 100 °C. Reaction conditions: 1.0 g IL, 68 mg (0.54 mmol) HMF, 100 mg catalyst (2.5 wt% Ru, 0.025 mmol), 100 °C, ambient air pressure.

The corresponding reaction for $Ru(OH)_x/La_2O_3$ exhibited a different pattern. As can be seen in Figure 4.30 the maximum yield of 57 % was obtained already after 6 hours, where after it slowly declined. However, this was a consequense of FDA being formed as the reaction progressed, ending with an FDA yield of 8 % after 30 hours.

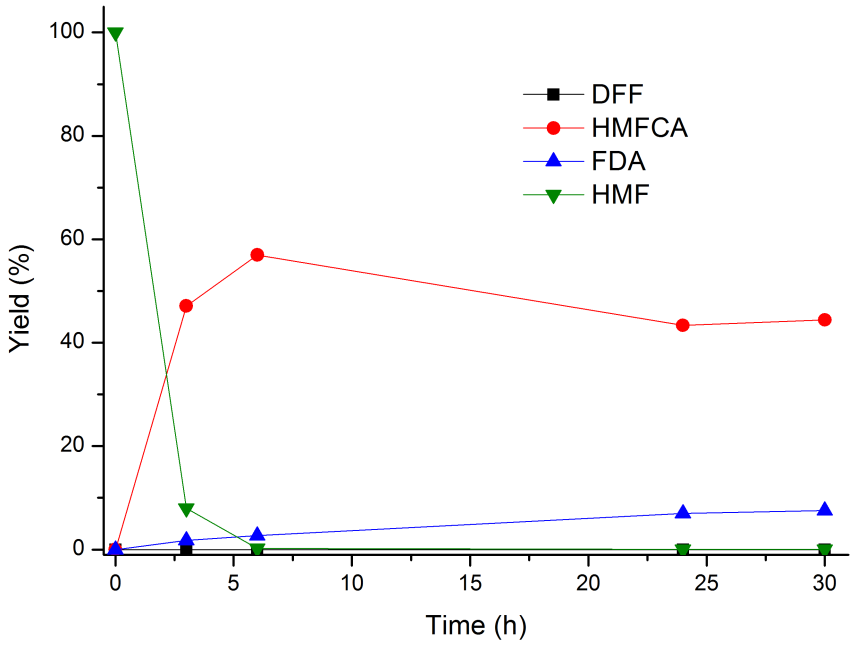


Figure 4.30. Oxidation of HMF with $Ru(OH)_x/La_2O_3$ in [EMIm][OAc] at 100 °C. Reaction conditions: 1.0 g IL, 68 mg (0.54 mmol) HMF, 100 mg catalyst (2.5 wt% Ru, 0.025 mmol), 100 °C, ambient air pressure.

4.5 Oxidation of HMF at High Pressure

The oxidation reactions had so far given interesting results with different product distribution and yields depending on catalyst support and on IL. Nonetheless, the yields were far from satisfactory for developing a process at scale and an investigation of the oxidations at higher pressure with pure dioxygen was therefore conducted. A reaction temperature was between 100 and 140 °C was chosen along with a reaction time 5 hours. The results of the high pressure experiments are summarized in Table 4.7.

The first high pressure experiments (entry 1 and 2) were conducted at 140 °C with 10 bars of dioxygen. For [EMIm][HSO_4] together with $Ru(OH)_x$/spinel (entry 1) a quite low conversion could be seen along with negligible yields of both HMFCA and FDA. This was consistent with the results at ambient pressure where no oxidation products were obtained. A slight improvement of the experiment at ambient pressure was $Ru(OH)_x/La_2O_3$ in [EMIm][OAc] (entry 2) where an FDA yield of 14 % was obtained compared 9 % at ambient conditions. This was at the expense of HMFCA, the yield of which was 4 %, compared to 30 % at ambient pressure. In accordance with the results at ambient pressure, the

Table 4.7: HMF oxidation in different ILs with $Ru(OH)_x$ on various supports as catalyst.[a]

					Conversion (%)		Yield (%)		
Entry	Ionic liquid	Catalyst	$P\ O_2$ (bar)	T (°C)	HMF	FA	DFF	HMFCA	FDA
1	$[EMIm][HSO_4]$	$Ru(OH)_x$/spinel	10	140	58	0	3	1	0
2	[EMIm][OAc]	$Ru(OH)_x$/spinel	10	140	>99	0	0	4	14
3	$[EMIm][HSO_4]$	$Ru(OH)_x$/HT	10	100	32	0	18	3	0
4	[EMIm][OAc]	$Ru(OH)_x/La_2O_3$	10	100	97	31	0	34	23
5	$[Bu_3MeN][MeOSO_3]$	$Ru(OH)_x$/HT	30	100	60	0	26	16	1
6	$[Bu_3MeN][MeOSO_3]$	$Ru(OH)_x$/spinel	30	100	62	0	18	26	3
7	$[EMIm][HSO_4]$	$Ru(OH)_x$/HT	30	100	52	0	25	8	0
8	[EMIm][OAc]	$Ru(OH)_x/La_2O_3$	30	100	98	30	0	12	48

[a] Reaction conditions: 12 g IL, 350 mg (2.78 mmol) HMF, 0.5 g catalyst (2.5 wt% Ru, 0.125 mmol), 5 hours.

temperature was decreased to 100 °C in order to lower the impact of HMF degradation. This led to a sharp increase in yield for $Ru(OH)_x/La_2O_3$ in [EMIm][OAc] (entry 4) where the HMFCA and FDA yield now amounted to 34 and 23 % respectively. In addition to this, a substantial amount of formic acid was formed, which was most likely a consequence of some form of oxidative degradation of HMF or the other reaction intermediates. For $[EMIm][HSO_4]$ in combination with $Ru(OH)_x$/HT (entry 3) a very low conversion was observed and the major product was DFF with 18 % yield.

The pressure was increased even further to 30 bar of dioxygen to obtain higher conversion of the unreacted HMFCA. The effects of the pressure increase can be seen in entries 5-8. For $[Bu_3MeN][MeOSO_3]$ and $[EMIm][HSO_4]$ a higher conversion was observed, resulting in an increase of DFF and HMFCA, whereas FDA yields were still very low. The reaction mixtures for these IL/catalyst systems (entries 5-7) were very viscous, thus limiting gas mass transfer and consequently effecting yields. For [EMIm][OAc] in combination with $Ru(OH)_x/La_2O_3$ the highest yield so far was observed with 12 % of HMFCA and 48 % FDA. An additional 30 % formic acid was also formed.

4.5.1 Leaching Study

The combination of high temperature and ILs are very rough conditions, making leaching of catalytic species to the bulk a possible risk. A homogeneous mechanism was also confirmed in some ILs by the use $RuCl_3$ which gave comparable yields to the best solid catalysts. Leaching tests were therefore performed for $Ru(OH)_x/La_2O_3$ and $Ru(OH)_x$/spinel in [EMIm][OAc]. The catalysts were

stirred with the IL at 100 °C and then filtered off. The resulting IL received a black color indicating dissolution of ruthenium. The IL was reacted with HMF in open tubes for 24 hours at 100 °C and ambient pressure affording the results shown in Table 4.8. The results showed clearly that major leaching of the active catalyst had taken place and consequently oxidizing HMF homogeneously. The yields are comparable to the corresponding yields using the solid catalysts (Figure 4.29 and Figure 4.30) which implies that the reaction was partly catalyzed by dissolved ruthenium species.

Table 4.8: HMF oxidation in [EMIm][OAc] filtered off from $Ru(OH)_x/La_2O_3$ and $Ru(OH)_x$/spinel.[a]

		Conversion (%)	Yield (%)		
Entry	Catalyst	HMF	DFF	HMFCA	FDA
1	$Ru(OH)_x/La_2O_3$	100	0	44	4
2	$Ru(OH)_x$/spinel	100	0	44	4

[a] Reaction conditions: 1.0 g [EMIm][OAc], 68 mg (0.54 mmol) HMF, 100 °C, 24 hours, ambient air pressure.

4.6 Conclusions

The lower performance of some catalysts in the study shown herein could be a consequence of a higher stability which prevents leakage. A heterogeneous mechanism in the ILs cannot be ruled out, even though the yields of the leakage tests were comparable to the ones using the normal procedure with the heterogeneous catalyst.

In order to find a successful and suitable catalyst for large scale purposes for FDA production in ILs it would most likely benefit from being a homogeneous water soluble catalyst. This would enable an easy recovery of FDA after complete reaction by crystallization from water. The catalyst and IL would end up in the mother liquid and after removal of water the IL/catalyst system could be recycled for the next batch. A heterogeneous catalyst could still be an option if one with high resistance to the ILs in question could be obtained. Evidently, the catalysts presented herein prepared by the deposition-precipitation method make out catalysts that cannot withstand the combination of ILs even at moderate

temperatures. Alternative heterogeneous aerobic catalysts would be of interest in a further study of this reaction as well as the study of other aerobic oxidations in ILs. The advantage of using an IL as solvent for aerobic oxidations with heterogeneous catalysts is obvious when your product or any of the reactants have low solubility in conventional solvents.

4.7 Experimental

4.7.1 Materials

5-(Hydroxymethyl)furfural (HMF) (>99%), 2-furoic acid (98%), levulinic acid (LA) (98%), formic acid (FA) (98%), ruthenium(III) chloride (purum), magnetite (>98%), $Ca_5(PO_4)_3(OH)$ (HAp) (>97%), aluminium oxide (>99.9%), $Mg_6Al_2CO_3(OH)_{16}{\cdot}4H_2O$ (HT), zirconium oxide (99%), lanthanum(III) nitrate hexahydrate (99.99%) and sodium hydroxide (>98%) were acquired from Sigma-Aldrich. Ruthenium(III) nitrate hexahydrate (99.9%) and magnesium nitrate hexahydrate (p.a.) were obtained from Merck. Cerium oxide (99.5%) and lanthanum(III) oxide (99.9%) were purchased from Alfa Aesar. Magnesium oxide (p.a.) was purchased from Riedel-de Haën AG. 2,5-Diformylfuran (DFF) (98%) was obtained from ABCR GmbH & Co. 2,5-Furandicarboxylic acid (FDA) (>99%) and 5-hydroxymethyl-2-furan-carboxylic acid (HMFCA) (>99%) were purchased from Toronto Research Chemicals Inc. and dioxygen (99,5%) from Air Liquide Denmark. The ionic liquids 1-ethyl-3-methylimidazolium dicyanamide ([EMIm][$(CN)_2$]) (98 %) and 1,3-dimethylimidazolium dimethylphosphate ([MMIm]-[dmp]) (98 %) were purchased from Solvent Innovation, while all other ionic liquids were obtained from BASF (>95 %). All chemicals were used as received. All $Ru(OH)_x$/support catalysts were synthesized according to literature procedures.[180]

4.7.2 Apparatus and Analysis

The catalytic screening experiments at ambient pressure were performed using a Radley Carousel 12 Plus Basic System, while high pressure oxidation reactions were carried out in stirred Parr autoclaves equipped with internal thermocontrol (T316 steel, Teflon^{TM} beaker insert, 100 ml). All samples were analyzed by HPLC (Agilent 1200 series, Bio-Rad Aminex HPX-87H, 300 mm x 7.8 mm pre-packed column, 0.005 M H_2SO_4 mobile phase, 60 °C, 0.6 mL/min).

The yields and selectivities were based on conversion of HMF and confirmed by

calibration of standard solutions of the products and reactants involved.

$$\texttt{HMF conversion} = \frac{1 - \texttt{(HMF concentration in product)}}{\texttt{Starting amount of HMF}} \tag{4.1}$$

$$\texttt{Yield FDA/HMFCA/DFF} = \frac{\texttt{Amount of FDA/HMFCA/DFF}}{\texttt{Starting amount of HMF}} \tag{4.2}$$

4.7.3 Oxidation procedures

In catalytic screening experiments performed at ambient pressure, catalyst (100 mg, 0.025 mmol Ru) and IL (1.0 g) were mixed in a 40 mL tube and stirred at 140 °C for 10 minutes. HMF (70 mg, 0.56 mmol) was added and the mixture was stirred in an open flask for 24 hours. The reaction was cooled down to ambient temperature and diluted to 10 mL with 0.1 M NaOH. The catalyst was filtered off and the resultant solution analyzed by HPLC.

In high pressure oxidation reactions, catalyst (0.5 g, 0.125 mmol Ru), HMF (350 mg, 2.78 mmol) and IL (12.0 g) were mixed in a Parr autoclave, pressurized with dioxygen (10 bar) and stirred at 140 °C for 5 hours. The reaction was cooled down to ambient temperature and diluted to 100 mL with 0.1 M NaOH. The catalyst was filtered off and the resultant solution analyzed by HPLC.

4.7.4 Procedure for leaching test

Catalyst (100 mg, 0.025 mmol Ru) and [EMIm][OAc] (1.0 g) were mixed in a 40 mL tube and stirred at 100 °C for 3 hours. The catalyst was filtered off affording a black colored liquid. HMF (70 mg, 0.56 mmol) was added to the liquid and the mixture was stirred in an open flask at 100 °C for 24 hours. The reaction was cooled down to ambient temperature, diluted to 10 mL with 0.1 M NaOH, filtered and analyzed by HPLC.

Process Development for Production of 5-(Hydroxymethyl)furfural in Ionic Liquids

5.1 Introduction

The use of ILs as reaction media for the conversion of biomass to chemicals has so far been limited to the laboratory. The majority of the research articles published on HMF production in ILs has focused on finding different catalytic systems to enhance the selectivity for both fructose and glucose conversion to HMF. If the research on HMF synthesis in ILs is to remain of interest to the researchers on HMF production, more studies on large scale processes are needed.

A few examples of large scale processes for the production of HMF in conventional solvents can be found in the literature. Most of these are described in a review by Kuster[19] from 1990 where the processes thus far are summarized. Two recent publications also deserve mentioning. The integration of enzymatic and acid catalysis in aqueous solution was described by Huang et al,[86] where glucose was converted enzymatically to fructose, which was enriched with boric acid. The formed fructose was then dehydrated to HMF using a biphasic system with 1-butanol in combination with NaCl as phase modifier. An analysis based on technological and economical parameters was recently made for the production of HMF using a biphasic system with fructose as feedstock.[181] The main conclusion drawn by the authors was that the minimum selling price for HMF

was very sensitive to the price of fructose and the selectivity for the dehydration reaction. To date, no assessment of an IL-based process for HMF production has been made, which prompted us to model a process taking economical, chemical and technological aspects into account.

5.2 Process Design

When developing a process for HMF synthesis in ILs a few different alternatives can be envisioned. We chose to consider three options: a biphasic process, a single phase process with extraction of the product by an organic solvent and a single phase process with distillation of the product after reaction. The three different alternatives are discussed briefly below:

5.2.1 Biphasic Process

A schematic overview of a biphasic process is depicted in Figure 5.31. This would be parallel to a biphasic processes for water/organic solvent systems.[15] The feedstock would be dissolved in the IL in the dissolution tank together with catalyst and then pumped over to the biphasic reactor. Extraction solvent (e.g. MIBK, EtOAc) would be added and the reaction would proceed at elevated temperature, possibly leading to super-ambient pressure depending on solvent. Ideally, the product would exclusively end up in the organic solvent and separated in the subsequent phase settler. The IL would then be pumped to an evaporator, stripped of water, pumped back to the dissolution tank and be recycled for the next batch. The extraction solvent would be removed by distillation affording crude HMF.

5.2.2 Single-Phase Process with Product Extraction

The process scheme of a single phase process with product extraction is shown in Figure 5.32. The main difference from the biphasic process is that the reaction would proceed in a single IL phase. After complete conversion, the reaction mixture would be transferred to a separation tank where extraction solvents would be added and the product extracted. The IL and product solution would

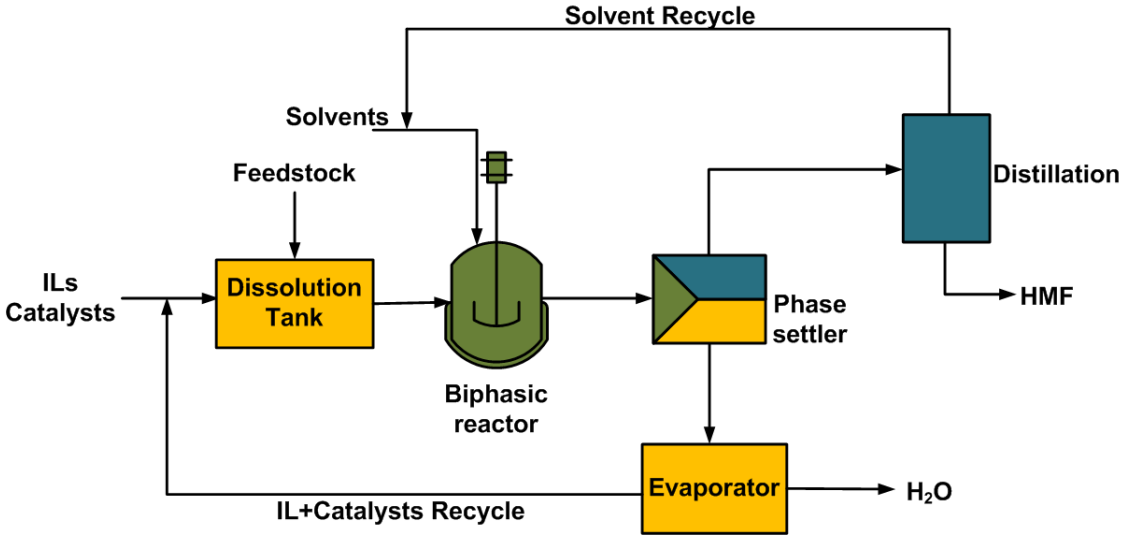


Figure 5.31. Biphasic process.[42]

then be separated as in the biphasic process.

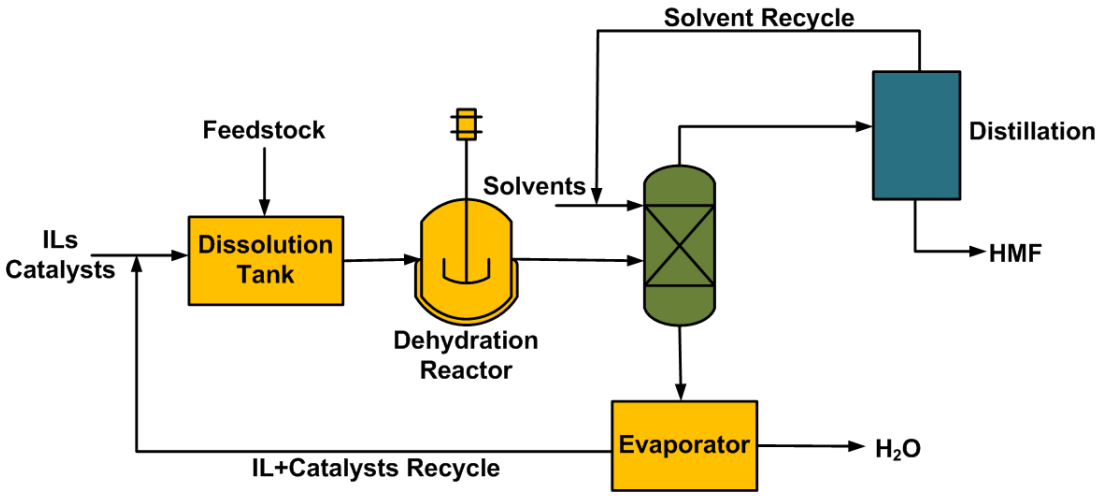


Figure 5.32. Single-phase process.[42]

5.2.3 Single-Phase Process with Product Distillation

A more simple process compared to the two mentioned above could also be envisioned. This is illustrated in Figure 5.33, where a single phase process with a product recovery enabled by distillation would result in a simple process scheme with fewer unit operations and no solvent apart from IL is utilized. The boiling point of HMF is 85-88 °C at 0.01 Torr[182] which should make distillation possible with appropriate equipment. The negligible vapor pressure of the IL offers the unique opportunity to remove the product by distillation without any loss

of the reaction media. Recovery of HMF by distillation would require further experimental investigation.

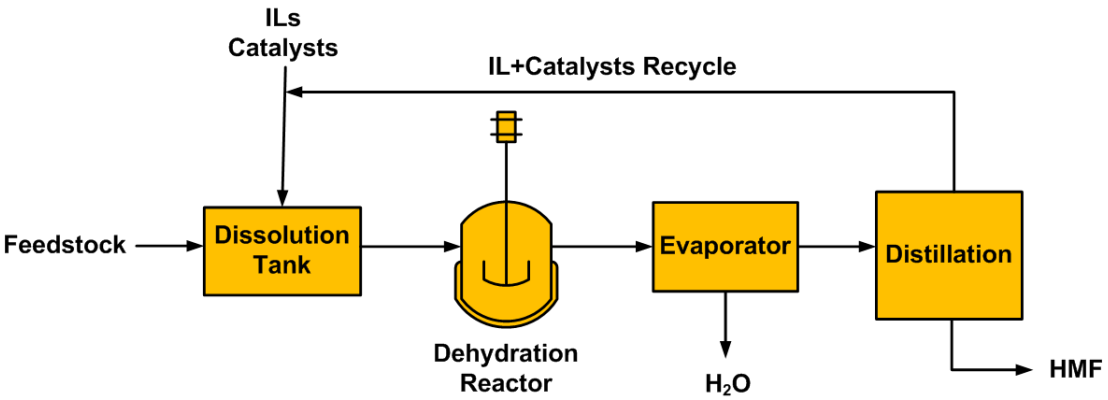


Figure 5.33. Single-phase process with distillation of HMF in the final step.[42]

5.3 Assessment of Biphasic HMF Process

After considering the different process schemes, we decided to use the single phase process with product extraction (Figure 5.32). This was based on the assumption that this was the most feasible of the three and that sufficient experimental data could be obtained from literature. The new catalytic systems developed and described in Chapter 3 was unfortunately at this stage considered to be inferior in terms of selectivity and yield. We chose to use the work by Yong et al.[63] for our model because of the excellent yields for both fructose and glucose dehydration. Their study consisted of a [BMIm]Cl-based system using chromium carbenes as catalysts. The issue of chromium toxicity was not dismissed, but the assumption that all catalyst could be recycled back was considered good enough for this case study. As extraction solvent the choice fell on ethyl acetate (EtOAc) because it is considered to be non-toxic and easily obtained from renewables. It also has a boiling point of 77 °C making the energy needed to remove it lower than for MIBK (bp 117-118 °C), which is another commonly employed extraction solvent for HMF. We then chose four different process scenarios according to the process model summarized in Table 5.9; one using fructose as feedstock at low concentration, one starting from fructose at high concentration, one starting from glucose at low concentration and finally one starting from glucose at high

concentration. It was reported that as much as 50 wt% of sugar could be used without significantly affecting yield, which offered a great advantage for an IL-based process.[63]

Table 5.9: The four different scenarios chosen with the reported feedstock concentration and corresponding selectivity and conversion.[63]

Scenario	Feedstock	Feed concentration (wt%)	Selectivity	Conversion
F1	Fructose	17	96	100
F2	Fructose	50	70	100
G1	Glucose	17	81	100
G2	Glucose	50	73	100

The complete methodology for the process assessment can be found in Appendix.

5.4 Results and Discussion

In the dehydration experiments, HMF had proven to be tightly bound to [BMIm]Cl and [EMIm]Cl that the addition of water was required to efficiently remove HMF by extraction with EtOAc. Different compositions of HMF/IL/H_2O/EtOAc were studied in order to find the best ratio between the different components for the most efficient extraction. These compositions were investigated at 30, 50 and 70 °C. The results of the extraction studies are shown in Figure 5.34. It was clear that the ratio of water/IL was the most significant parameter for the R-value. The temperature had no influence by comparison. Based on these results we chose 50 °C with and a water/IL ratio equal to 1. The extraction temperature of 70 °C was considered to be to close to the boiling point of EtOAc and 30 °C would require a larger energy input by first cooling prior to extraction, followed by heating for evaporation. The IL/water ratio was chosen based on the assumption that it was better to use less water and more extraction solvent since water removal requires more energy.

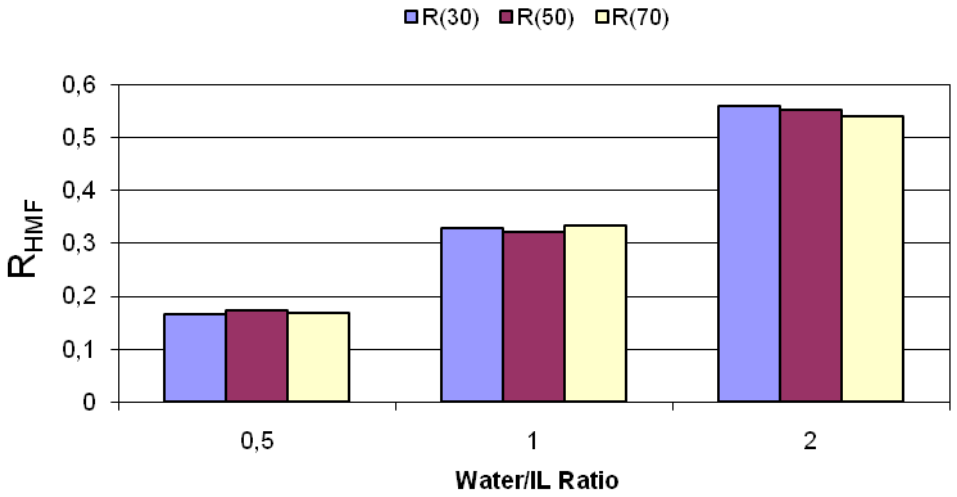


Figure 5.34. Effects of the water/IL volume ratio and temperature on the partition coefficient.

Based on the prerequisites described in the process design section with the four different scenarios, a cost distribution was calculated which is shown in Table 5.10 and Figure 5.35. At this stage IL and catalyst cost was disregarded. The capital investment cost was similar for scenarios with the same feed concentration, and those with low feed concentration (F1 and G1) had higher cost than high feed concentration (F2 and G2). An important conclusion from the cost distribution analysis was that the cost for the processes using glucose as feedstock (G1 and G2) was cheaper than the ones using fructose as feedstock (F1 and F2). For all scenarios the largest part of the overall cost was the feedstock. Notably, for G2 the lower cost from utilities because of higher concentration resulted in an overall decrease of production cost compared to G1 in spite of the decrease in selectivity associated with higher concentration. For F2 the reduction in utility cost did not pay back what was lost from impaired selectivity, resulting in a similar overall production cost compared to F1.

Table 5.10: HMF production cost without adding IL and catalyst cost for the four process options.

Item	HMF production cost US$			
	F1	F2	G1	G2
Glucose/Fructose	0.76	1.04	0.54	0.60
Solvent	0.05	0.05	0.05	0.05
Steam (MP 200 Pigs)	0.31	0.13	0.37	0.12
Cooling water	0.03	0.01	0.03	0.01
Labor and Labor supervision	0.08	0.08	0.08	0.08
Other variable cost	0.11	0.10	0.10	0.07
Fixed cost	0.06	0.04	0.07	0.04
Plant overhead cost	0.06	0.05	0.06	0.05
General expense	0.12	0.13	0.11	0.09
Total	1.58	1.62	1.42	1.12

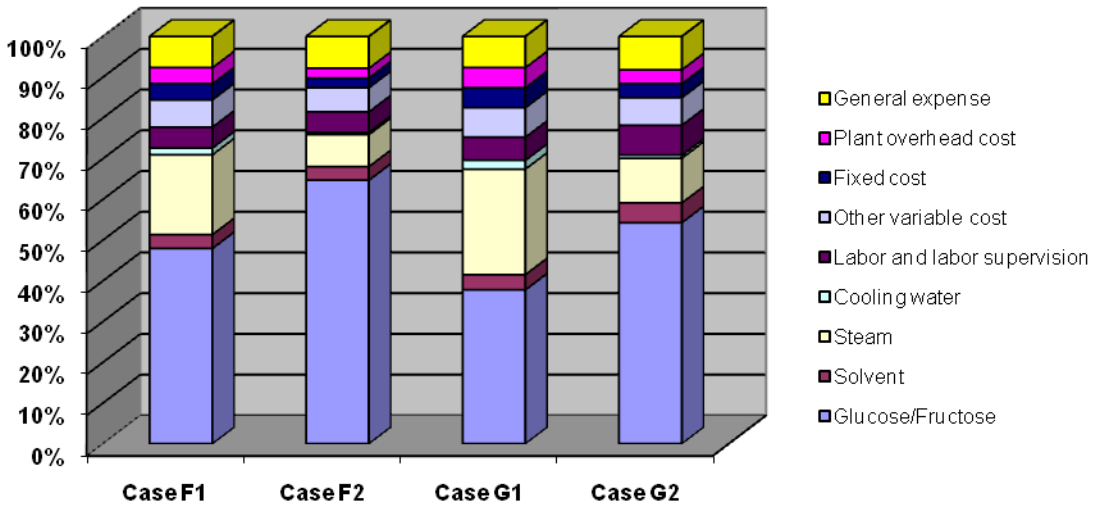


Figure 5.35. Cost distribution for HMF production cost without adding IL and catalyst cost.

With the production cost at hand the price of IL was included to evaluate the number of recycles required to obtain a cost competitive process. The IL-system which we chose for this assessment was only recycled 7 times in the reported study,[63] which is far from enough considering the current cost of [BMIm]Cl. Assuming a [BMIm]Cl cost of 11 US$ and a catalyst cost of 2 US$, the effect of IL-reuse was plotted to give the production cost of HMF as a function of number of IL-cycles which is shown in Figure 5.36. For comparison, the production cost

of a biphasic MIBK/water system with fructose as feedstock was included in the graph.[15] It was assumed that HMF selectivity was not hampered when recycling the IL. Evidently, a large number of recycles was necessary to obtain an economical process. The production cost decreased drastically until the number of cycles reached 50 after which a more slow decrease was observed. After 150 cycles the cost of feedstock became more significant than the cost of IL. After reaching 200 cycles the HMF production cost for F1, F2, G1 and G2 was 1.97, 1.74, 1.88 and 1.23 US$ respectively. As expected, the high-concentration scenarios were superior in cost effectiveness. Another noteworthy result was that the biphasic MIBK/water system was more cost competitive in comparison to all scenarios except G2. In order for G2 to be cheaper than the biphasic system, 45 recycles of IL was required.

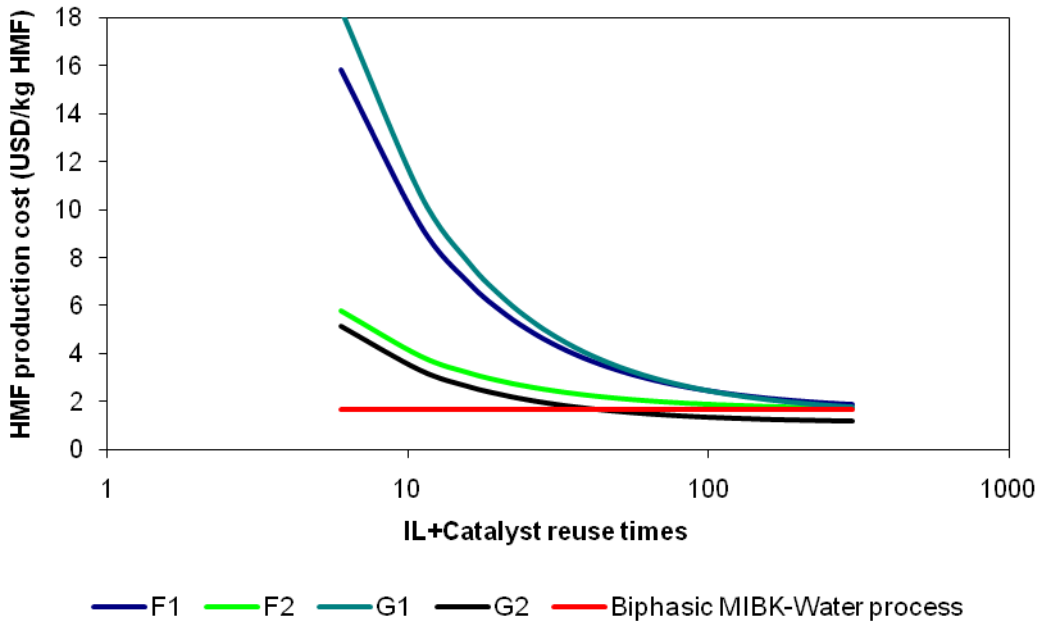


Figure 5.36. HMF production cost as a function of the number of IL + catalyst recycles.

The results presented above concluded that G2 was the most cost competitive process scenario using [BMIm]Cl as solvent with a chromium carbene catalyst system. The total cost breakdown was calculated for an IL/catalyst reuse of 200 times and is shown in Figure 5.37. The dominating cost was naturally the raw material glucose (49 %). This was in alignment with the recent assesment of a

biphasic MIBK/water process where fructose was found to dominate the cost.[181] The cost of glucose was followed by the cost of utilities (steam and cooling water) which amounted to 11 %. The combined cost for IL and catalyst was 10 % and all cost related to capital investment was around 9 %. A calculation of the effect

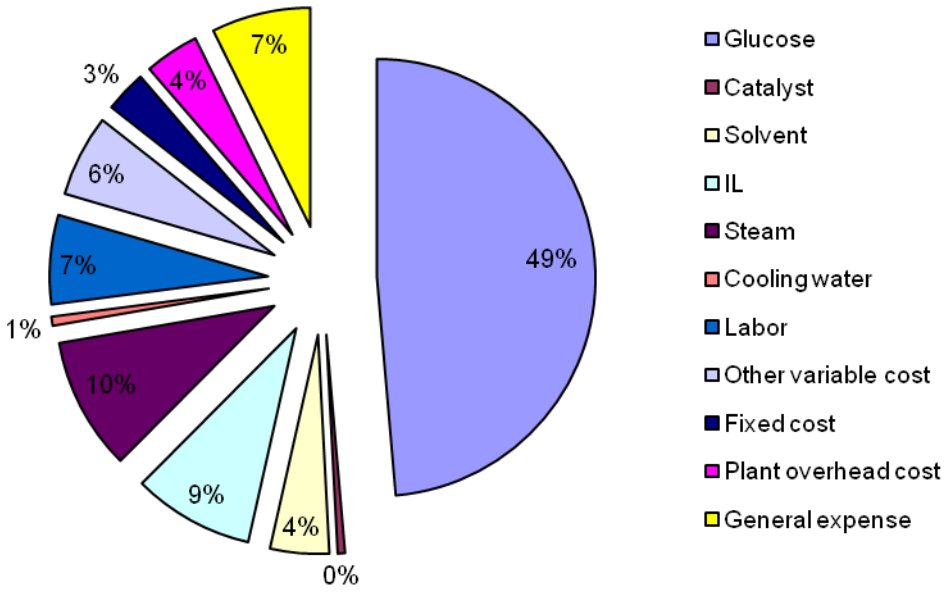


Figure 5.37. Total HMF production cost breakdown. The production cost is obtained by using the process option G2 with an IL and catalyst recycle of 200 times.

for the production cost by an increase in selectivity of the reaction was also made. As can be seen in Figure 5.38, improving the selectivity to 93 % would result in a production cost below 1 US$ per kg. Evidently, improving selectivity has an impact on the overall process economy, accentuating the necessity of improved chemistry for HMF synthesis.

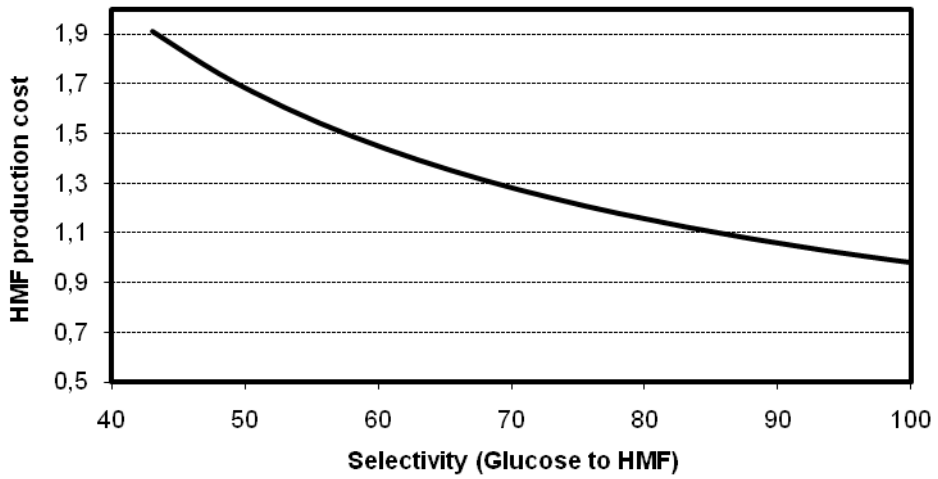


Figure 5.38. The HMF production cost as a function of the selectivity of the dehydration reaction.

5.5 Purification of HMF

Few papers and patents discuss the actual isolation of HMF from the ILs, something which is crucial for most applications. Furthermore, there is surprisingly little on the purification of HMF, another vital aspect of large scale production. Even though the exact future application of HMF at this stage is unknown, a robust purification protocol would be of the essence. A few examples can be found in the literature such as purification by distillation, chromatography and crystallization. However, these methods either involve the use of environmentally questionable solvents such as CH_2Cl_2 or excessive solvent use. Moreover, many of the methods have insufficient data on purity. The limited amount of published purification procedures for HMF could be due to its low melting point making crystallization, the preferred purification method for large scale production, more difficult.

In our search for a crystallization procedure we screened a number of conventional organic solvents in order to crystallize HMF from a crude reaction mixture. From this survey MTBE turned out to be an excellent solvent for crystallization. When decreasing the temperature to -30 °C, white crystals of HMF was formed. These crystals could be filtered off and washed with MTBE and subsequently 1-pentane. The low boiling point of pentane enabled efficient drying of HMF without melting the crystals. The purity was found to be >99

% according to HPLC. This purification method could be of some importance if the future chemical industry demand HMF with a specific purity. Telescoped processes from dehydration directly to oxidation or hydrogenation need not necessarily require high purity HMF solutions, since the obtained derivatives would be expected to be easier purified. Nevertheless, at this stage it is very difficult to predict what the future specifications for HMF would be and a reproducable purification protocol is therefore of the essence.

5.6 Conclusions

The assessment of a process for HMF production shown herein points out some important parameters that needs to be further investigated prior to implementation at large scale. One of the key parameters in HMF production in ILs is the number of recycles of the IL required for a cost competitive process. In research papers concerning sugar dehydration the number of recycles is seldomly above 10. We have shown here that 45 cycles are required for the process to compete with the water/MIBK biphasic system and 200 cycles are required to obtain HMF at a cost of 1.23 US$/kg. The assumption that a recycled IL has retained selectivity is made for simplicity. Naturally, one would assume that at some point the catalytic system would suffer in efficiency when the amount of by-products accumulate. Nonetheless, there are no reports in the literature describing such a phenomena and it would hence be difficult to include such a parameter in the assessment. It should also be stressed that the number of cycles are based on an IL price of 11 US$/kg, which could decrease with increased demand, and hence the number of cycles required could be lower. The selectivity for the dehydration reaction was based on the results from the paper by Yong et al[63] and could be improved with a more thorough investigation employing fractional factorial design giving a more complete picture of the influence of each parameter. In addition to selectivity, the assessment also showed that making the reaction with high concentration of sugar gives the IL process a clear advantage.

Apart from the assessment of the single phase process using an extraction solvent to recover HMF, the option of the aforementioned distillation process remains. If satisfactory recovery of the produced HMF could be obtained by

distillation, this would by far be the best option. In such a process no additional extraction solvent would be needed, which would be more desirable from an environmental point of view.

5.7 Experimental

5.7.1 Extraction of HMF from [BMIm]Cl/H_2O

Extraction experiments were made with 12 different compositions as shown in Table 5.11. Phase separations of these compositions were investigated at 30, 50 and 70 °C. HMF was dissolved in [BMIm]Cl at 70 °C in a 100 mL round bottom-flask equipped with a condenser. Water was added and the temperature adjusted to 30 °C (50 and 70 °C). EtOAc was added and the biphasic mixture was stirred for 1 hour after which the two phases were left to equilibrate for 1 hour. Samples of 1 mL from each phase were collected and analyzed by HPLC (Agilent 1200 series, Bio-Rad Aminex HPX-87H, 300 mm x 7.8 mm pre-packed column, 0.005 M H_2SO_4 mobile phase, 60 °C, 0.6 mL/min). The amount of HMF was confirmed by calibration with standard solutions.

Table 5.11: The different compositions for the extraction experiments.

	1a-c	2a-c	3a-c	4a-c
HMF	0.312 g	0.711 g	1.077 g	4.850 g
[BMIm]Cl	10.0 g	10.0 g	10.0 g	10.0 g
H_2O	5, 10 or 20 mL	5, 10 or 20 mL	5, 10 or 20 mL	5, 10 or 20 mL
EtOAc	30 mL	30 mL	30 mL	30 mL

5.7.2 Crystallization of HMF

Crude HMF produced from literature procedure[37] was dissolved in 4 volumes (L solvent/kg product) of MTBE at room temperature. The temperature was decreased to -30 °C and after 30 minutes crystal formation was observed. The mixture was left to crystallize for 12 hours after which the crystals were filtered off at -30 °C. The crystals were washed with of 1-pentane (1 volume) and sucked dry (90 % yield, >99 % pure by HPLC).

Conclusions and Future Perspectives

The inevitable depletion of fossil sources for commodity chemicals and polymers was the incentive for the work presented in this thesis. The work was meant as an evaluation of the possibility of economically producing the high potential HMF from sugars and with that adding an important piece of the puzzle of the future biopetrochemical industry. This work has had the ambition of showing the possibilities and limitations of the use of ILs as a reaction media for such processes. It is clear that in terms of selectivity and the potential of using natural polymers as starting materials, the IL-based process has an immense advantage over processes in water and organic solvents. The modeling described in Chapter 5 showed that a high number of recycles is imperative for making a cost competitive process of HMF from glucose. The number of cycles can be reduced by a lower price of IL or improved selectivity for the reaction. In order to develop an industrially feasible process more studies focused on recycling of the IL is needed. This will disclose how the by-products remaining in the IL affects the catalytic performance when the number of cycles reaches higher numbers.

It was made clear in Chapter 2 and 3 that combining the enzymatically catalyzed isomerization with dehydration was most unlikely to be successful, since the solvent systems retaining enzyme activity are not applicable for dehydration and vice versa. The two new catalytic systems presented in this thesis, $YbCl_3$ and $B(OH)_3$ do not surmount what has previously been shown with $CrCl_3$, but reveal some interesting mechanistic aspects of the reaction. As described in Chapter 3 both the cation and the anion of the IL is of importance for the selective formation of HMF. More studies in order to gain insight regarding the

interaction between catalyst and IL could enable the design of more efficient catalytic systems than the ones existing to date. Such investigations would consist of computational modeling of the different catalytic systems where the solvent ions are taken into account. As mentioned in Chapter 3, a thorough investigation of different boronic acids could also be of interest. This would comprise of e g. Hammet studies of different aromatic boric acid derivatives, where the outcome of varying substituents influencing steric and electronic effects would be evaluated.

The aerobic oxidation of HMF to FDA proved to work well when using [EMIm][OAc] as solvent. Finding a heterogeneous catalyst that resists degradation in the IL would make this procedure advantageous in comparison to homogeneous systems, since recycling of the catalyst would be simplified. Nonetheless, a homogeneous system with a water soluble catalyst is a strong alternative provided that the catalyst can be recycled with the IL without activity loss. Future oxidation studies should continue focus on [EMIm][OAc] as solvent (or structurally related ILs) together with homogeneous and heterogeneous catalysts. The oxidation study also concluded that ILs suitable for the dehydration reaction had lower performance for the oxidation using ruthenium catalysts. Based on this, a telescoped process from glucose to FDA with the catalytic systems described in this work would be difficult to accomplish.

If the points regarding future work are pursued, the development of a large scale production process for HMF in IL-media is a feasible complement to existing industry in the future. In addition to the investigations concerning chemistry, a reduced IL price and an increase in price for the competing petrochemicals would most likely be necessary. HMF is occasionally dismissed as a potential platform chemical due to the difficulties in obtaining selectivity for its formation from sugars. Nevertheless, the molecule is a potential starting compound for many different and important derivatives and would therefore serve as a good complement to many other biopetrochemical platforms. Thus, future development of its chemistry and process development is of the essence.

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Appendix

7.1 Spectra

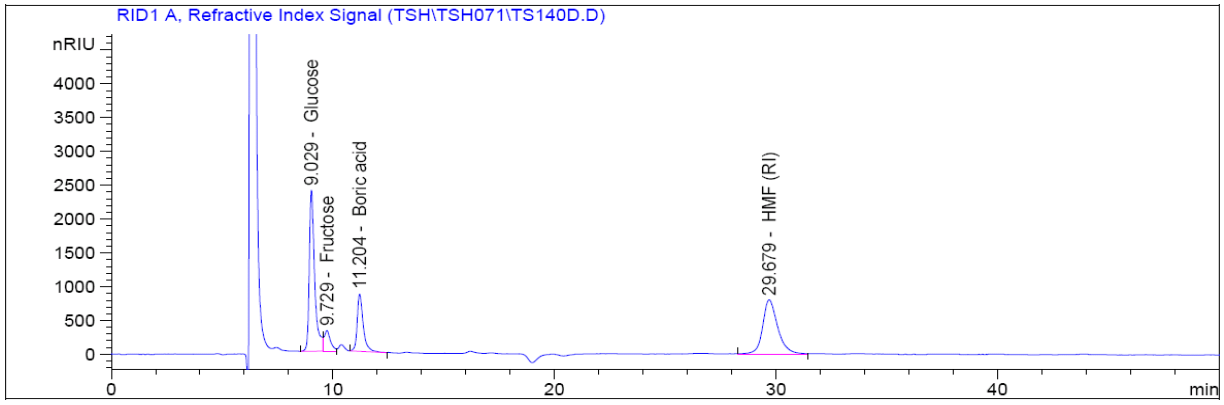


Figure A1. Refractive index HPLC chromatogram of a typical reaction mixture of the dehydration of glucose.

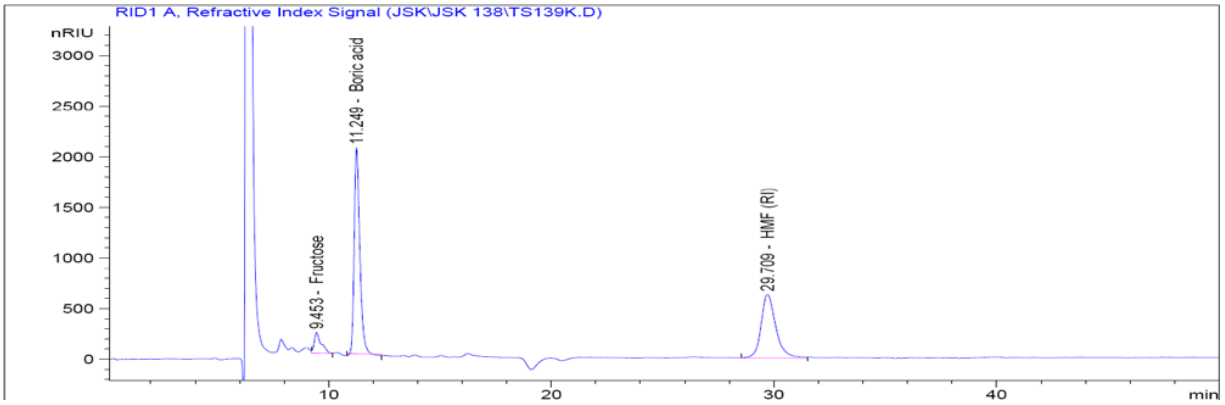


Figure A2. Refractive index HPLC chromatogram of a typical reaction mixture of the dehydration of fructose.

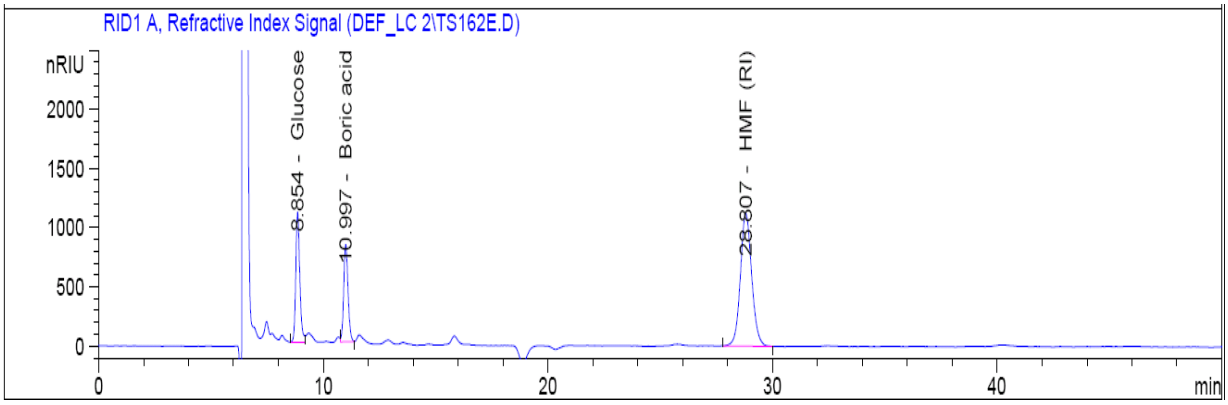


Figure A3. Refractive index HPLC chromatogram of a typical reaction mixture of the dehydration of maltose.

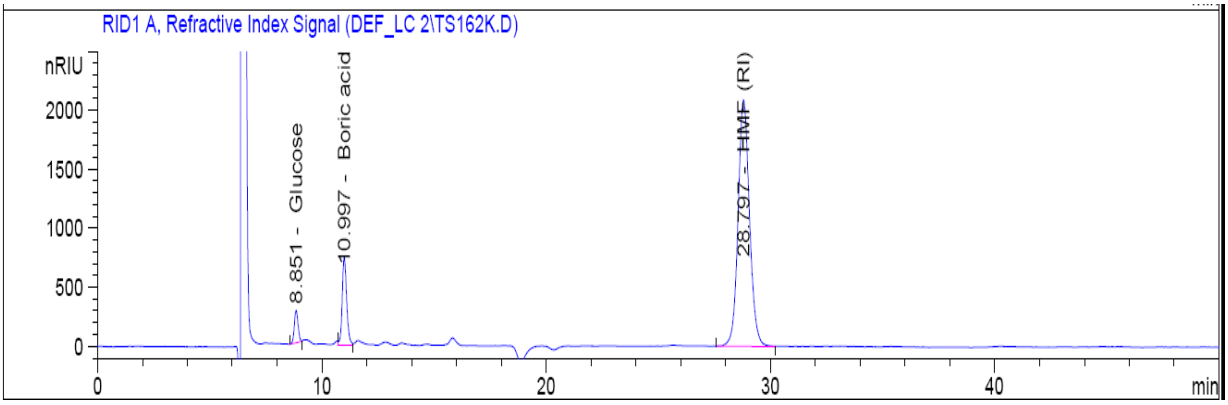


Figure A4. Refractive index HPLC chromatogram of a typical reaction mixture of the dehydration of sucrose.

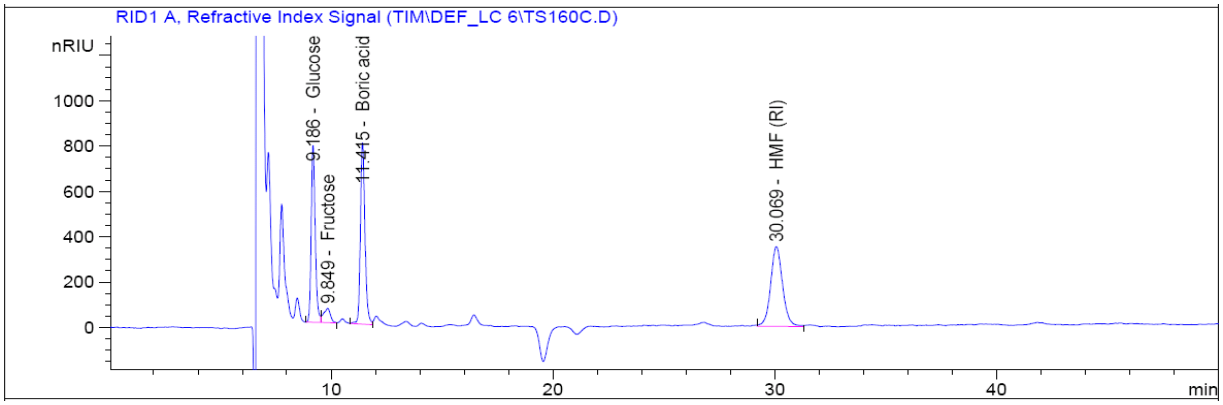


Figure A5. Refractive index HPLC chromatogram of a typical reaction mixture of the dehydration of starch.

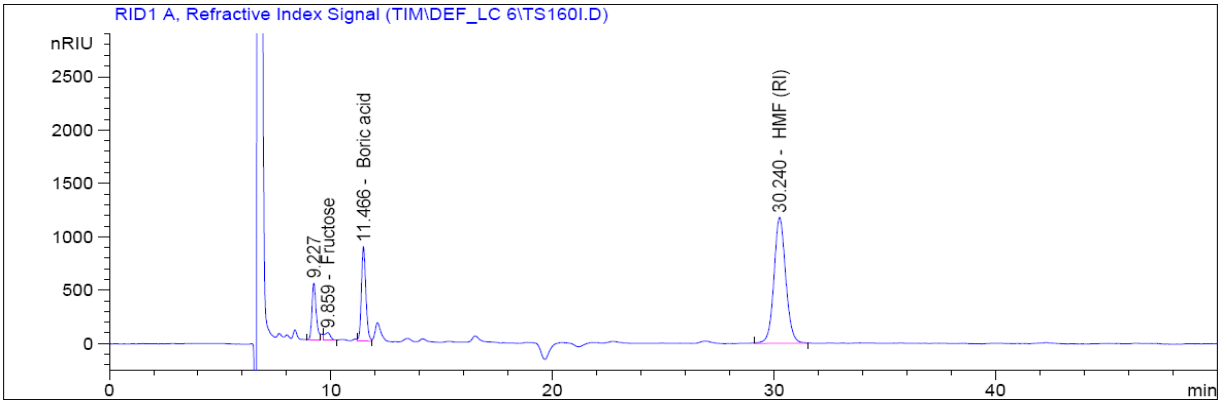


Figure A6. Refractive index HPLC chromatogram of a typical reaction mixture of the dehydration of cellulose.

The incorporation of deuterium in the aldehydic position of HMF was determined by 1H NMR (500 MHz) as follows. First, a T1 experiment was carried out on pure HMF and the relaxation times were determined to be below 6s for all protons in the molecule. Then a 1D scan was carried out with long relaxation time (32s) to ensure full relaxation. The resulting spectra are shown below.

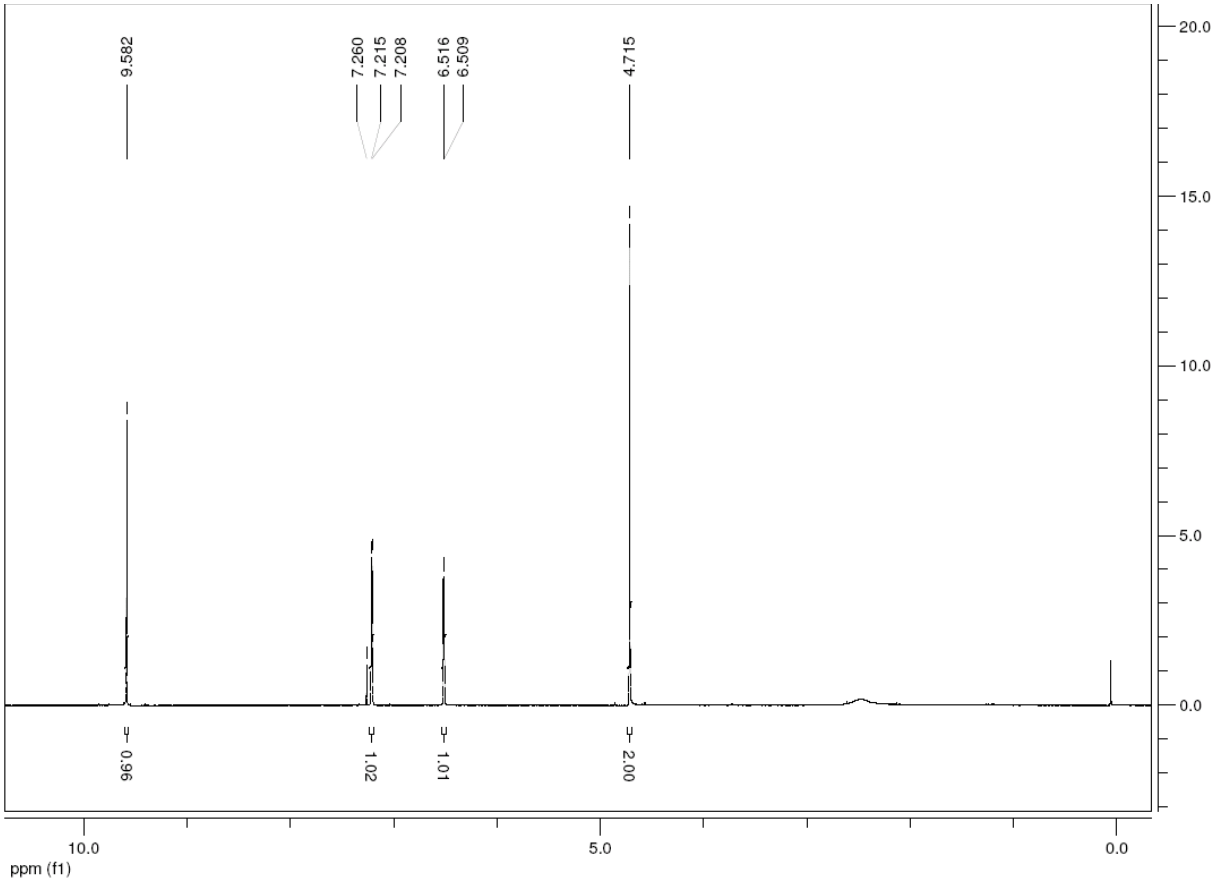


Figure A7. NMR spectra of HMF from normal glucose.

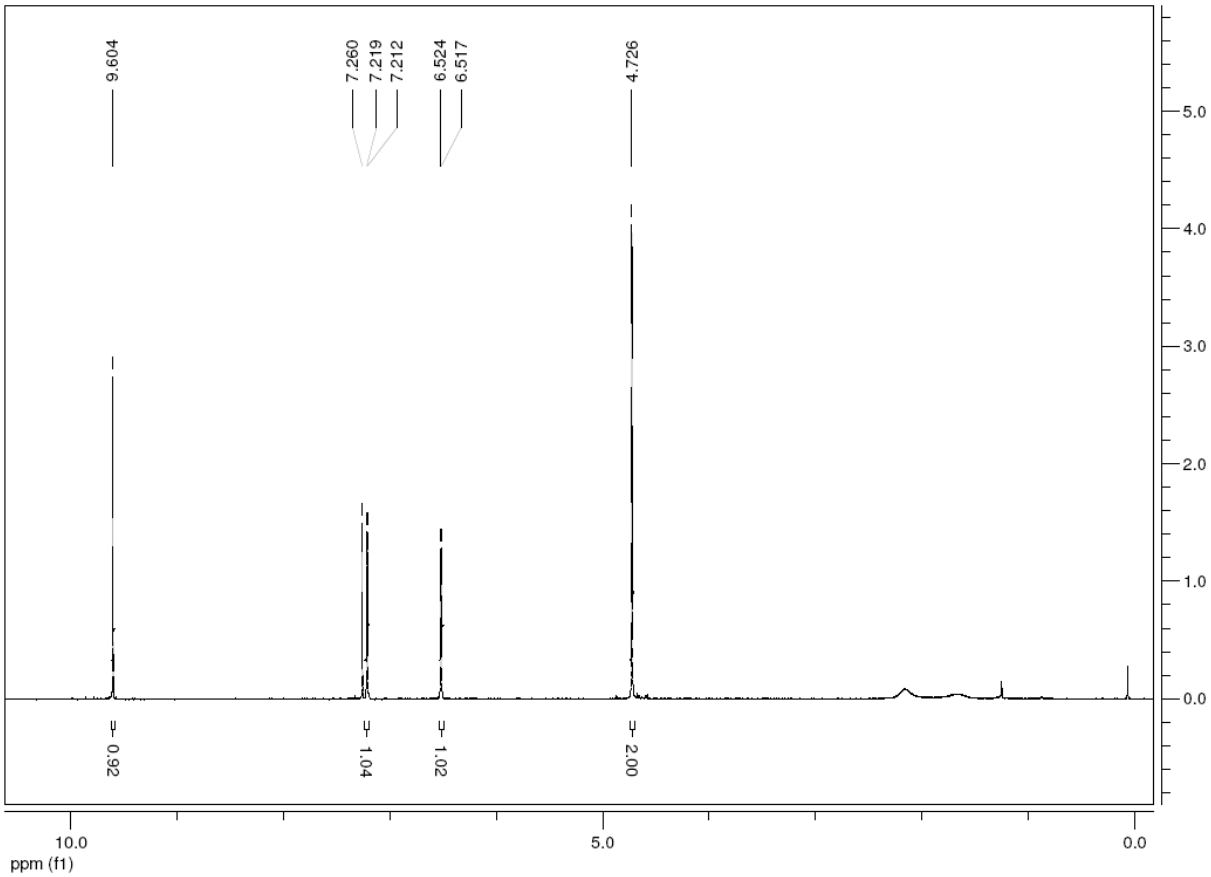


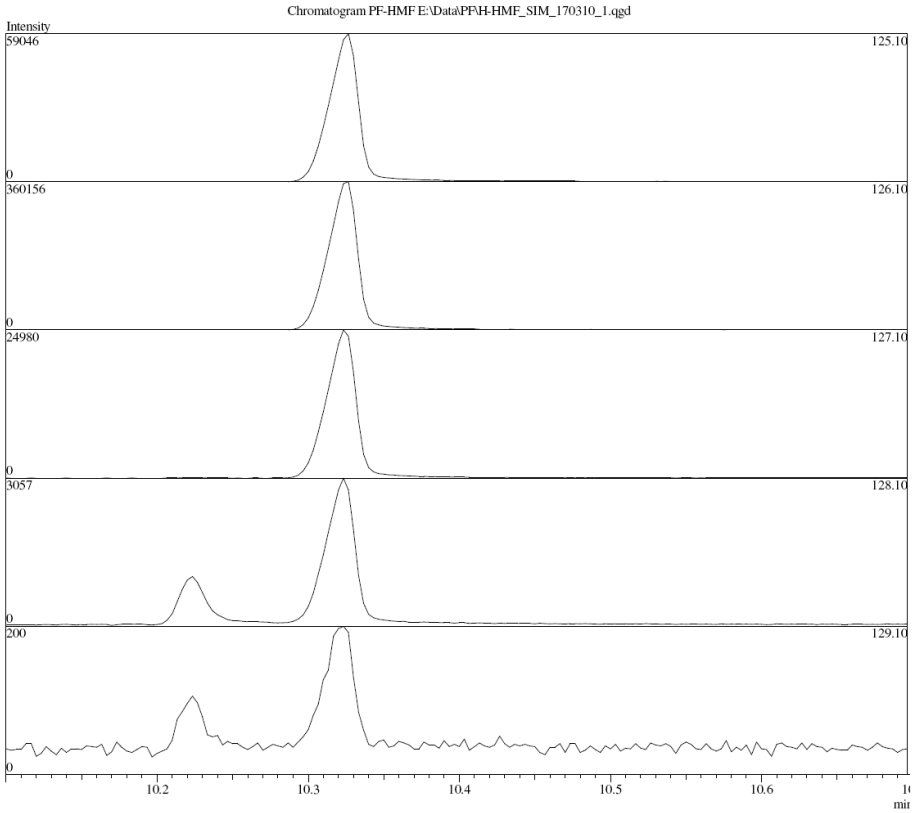
Figure A8. NMR spectra of HMF from glucose deuterated at C2.

The incorporation of deuterium in HMF was determined by GC-MS using a Shimadzu GCMS-QP2010S which was operated in single-ion monitoring (SIM) mode. The resulting spectra for M/Z=125.1, 126.1, 127.1, 128.1, and 129.1 were integrated. For the pure HMF the area of M+1 and M+2 peaks were determined and used to correct size of the combined peaks resulting from HMF and D-HMF.

04-05-2010 14:27:16

Sample Information

Analyzed by	: user advanced
Analyzed	: 17-03-2010 23:59:03
Sample Name	: PF-HMF
Sample ID	:
Vial #	: 5
Injection Volume	: 1
Data File	: E:\Data\PF\H-HMF_SIM_170310_1.qgd
Method File	: C:\GCMSsolution\Data\PF\60-280-18m_HMF_SIM.qgm
Report File	: C:\GCMSsolution\Data\PF\TIC_Spectrum_2 pages.qgr
Tuning File	: C:\GCMSsolution\System\Tune1\20100204.qgt



Quantitative Result Table

ID#	R.Time	m/z	Area	Name
1	10.326	125.10	81514	125.1
2	10.325	126.10	490501	126.1
3	10.324	127.10	34962	127.1
4	10.323	128.10	4242	128.1
5	10.323	129.10	263	129.1

Figure A9. GC/MS spectra of HMF from normal glucose.

Sample Information

Analyzed by	: user advanced
Analyzed	: 18-03-2010 00:23:51
Sample Name	: PF-D-HMF
Sample ID	:
Vial #	: 6
Injection Volume	: 1
Data File	: E:\Data\PF\D-HMF_SIM_170310_3.qgd
Method File	: C:\GCMSsolution\Data\PF\60-280-18m_HMF_SIM.qgm
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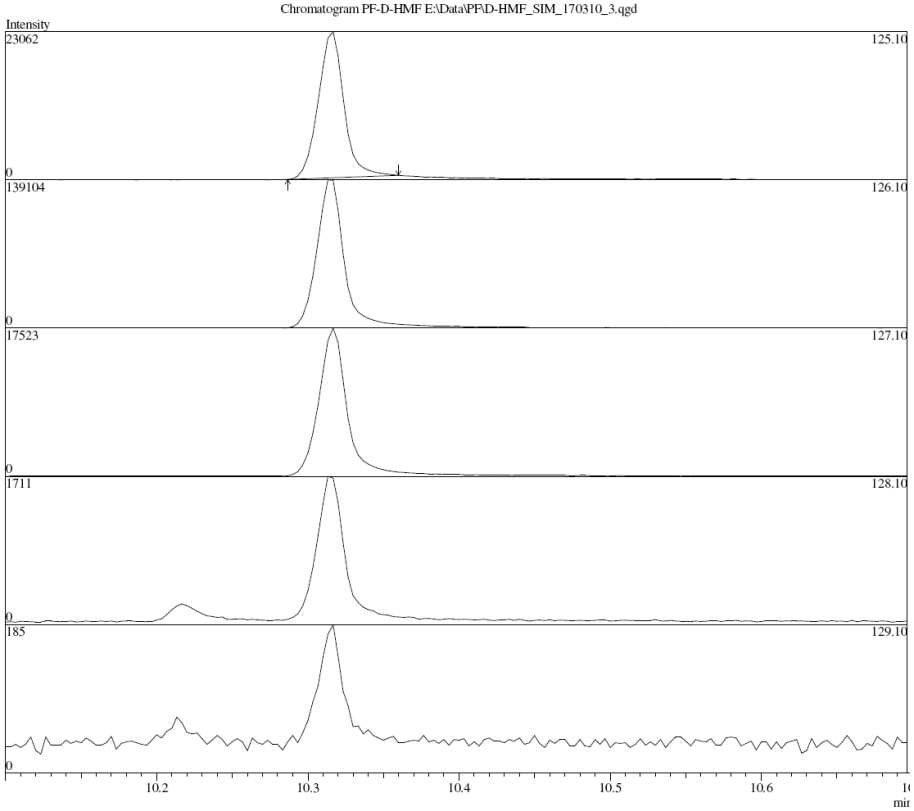
Tuning File	: C:\GCMSsolution\System\Tune1\20100204.qgt



Quantitative Result Table

ID#	R.Time	m/z	Area	Name
1	10.316	125.10	29609	125.1
2	10.315	126.10	184248	126.1
3	10.317	127.10	23431	127.1
4	10.315	128.10	2302	128.1
5	10.316	129.10	185	129.1

Figure A10. GC/MS spectra of HMF from glucose deuterated at C2.

7.2 Methodology for Process Assessment

Methods and Materials for Process Assessment

Mass balance

The basis for the mass balance is an output of 1 kg of final product. The calculation of process inputs (i.e. raw materials, reagents, process aids) and outputs (i.e., products, by-products, waste) were done using standard chemical engineering principles and based on the assumptions of each process units.

Liquid–liquid extractor (LLE)

The extraction process was designed by using a liquid-liquid extractor with designed extraction yield of 0.99 HMF/HMF. The designed extraction solvent volume of EtOAc is 4 times of the volume of IL+ H_20. For the calculations, equilibrium at each stage was assumed, thus the separation obtained in the extractor is related to the number of theoretical stages and can be calculated as:[183]

$$\frac{[HMF]_{(IL+H20)in}}{[HMF]_{(IL+H20)out}} = \frac{E^{N_S}(1-E)}{1-E^{N_S+1}} \qquad (2)$$

Where $[HMF]_{(IL+H20)in}$ and $[HMF]_{(IL+H20)out}$ are the mole concentration of HMF in the diluted reaction mixture enter and leave the extractor. E is the extraction factor can be calculated as:

$$E = \frac{\rho_{\mathrm{EtOAc}} V_{(IL+H20)in}}{R_{HMF}\rho_{IL+H20} V_{(\mathrm{EtOAc})in}} \qquad (3)$$

Where ρ_{EtOAc} and ρ_{IL+H20} are the density of the organic solvent and IL/water mixture and $V_{(\mathrm{EtOAc})in}$ and $V_{(IL+H20)in}$ are the volume of the extraction solvent and IL/water mixture.

Other assumptions hold for the calculation is that both phases must have the same residence time. The parameters in the extraction process are listed in Table A1.

Table A1. Summarized process parameters for second extraction column.

Second extraction	Extraction column
Extraction temperature (°C)	25
Extraction yield (mole HMF_{mibk}/mol $HMF_{aqueous\ in)}$	0.99
Phase feed volume ratio (MIBK/aqueous)	4
R_{HMF}	Experimental results of this work
ρ_{EtOAc} (kg/m^3)	897
ρ_{IL+H20} (kg/m^3)	1000

HMF Recovery (Solvent Evaporation)

In the unit operation, the designed process is based on the HMF recover yield of 0.99 mol HMF/mol HMF evaporation. We simulated the evaporation process in ProII 8.0.[184] Choosing a temperature at 55 ^{o}C, a pressure at 0.1atm, the simulation result showed that more than 99% HMF can be recovered with less than 1% lost in the vapor phase with EtOAc. The obtained HMF has a purity of 95 wt%. The solvent vapor phase after passing by the condenser and cooling to 50 ^{o}C, is recycled back to the extractor again.

IL and Catalyst Recovery (H_20 Evaporation)

Qi et al.[185] reported using vacuum oven to dry [BMIm]Cl with Amberlyst resin as catalyst at 60 ^{o}C for 24 hours and reported 7 times reuse of catalyst and IL. They did not observe any affect of yield during these 7 times reuse. Reusing [BMIm]Cl with HCl as catalyst for 6 times was also reported by Lai and Zhang[98] using vacuum oven at 50 ^{o}C. They also did not report any affects of yield. In this paper, we chose a vacuum evaporator (with 0.1 atm and 100 ^{o}C) to ensure all the water can be separated from IL and catalyst at short residence time. The vapor phase after condensing and cooling can be recovered as process water (with small amount EtOAc) and reuse again before extraction.

Energy balance

The energy required for cooling and heating for each individual unit operation were estimated using typical heat transfer equations. Process temperatures, pressures for estimate heating and cooling enthalpies were based on the process descriptions or conditions for the experiments taken place. The energy balance related with solvent evaporation and condensing was obtained directly from the simulation the process configuration in process simulator PROII.[184]

Economic Evaluation

To access the feasibility of using ionic liquid for HMF production in a large scale, and to compare different reaction options (F1, F2, G1 and G2), the economic analysis was performed. The economic analysis took into account the cost of the main units of the process (reactor, filter, extractor and evaporators) which is the base for the estimation of the total capital investment, main raw material (glucose/fructose, solvent, [BMIm]Cl and catalyst), utilities costs for the operation of the main units (energy and cooling water), the required labor cost and other expenses (such like plant overhead cost et al.). The designed plant has a capacity of 25,000 tons/year with 350 working days /year. The location is assumed in US and with the easy access to the raw material and energy supply therefore the transportation of raw material supply was not considered in this analysis.

Estimation of total capital investment (TCI)

With the designed capacity of the plant, and mass balance of the flowsheet, the size of equipments required in the flowsheet was estimated with the residence time of each unit.

Sizing, selection and design calculation of the equipments was calculated according to Perry and Green.[183] The cost of purchase the equipments was estimated according to Peters et al.[186] and www.matche.com.

The capital cost includes fixed capital investment (FCI) and working capital investment (WCI). Fixed capital cost (FCI) was calculated with an assumed percentage of total main unit cost (equation 4 and 5).[186]

$$TCI = FCI + WCI \quad (4)$$

$$FCI = E\sum(1 + f_1 + f_2 + f_3 + \ldots + f_n) \quad (5)$$

Where f_1, f_2, …, f_n are multiplying factors for piping, electrical, engineering and supervision etc. The detail the values used for estimation the total investment is listed in Table A1 in the appendix. Total capital investment was calculated based on the assumption that the fixed capital investment is 85% of TCI and the working capital is 15% of TCI.[186]

Estimation of total production cost

The total production cost (TPC) consists of the variable production cost, fixed charges, plant overhead costs and general expenses. The variable production cost includes raw material cost, catalysts and solvents cost, utilities (electricity, steam, process water and cooling water etc.), waste disposal cost, labor and labor supervision cost, plant maintenance and repair cost, operating supplies, laboratory charges, royalties and patent cost. The fixed charges include the taxes of the property, financing, rent, insurance and depreciation charge. Plant overhead cost is the cost directly related to the production operation.

The costs of raw material, solvent, catalysts, utilities and waste disposal were directly related with the mass and energy balance of the designed process. Labor requirements were estimated from the designed equipments in the plant using the method from Peters et al.[183] Other remaining variable costs, fixed cost without depreciation, plant overhead cost and general expenses were estimated with using typical percentage values. The depreciation was calculated with a constant yearly depreciation rate based on a 10 year schedule.

Table A2. Typical percentage values for estimation capital investment based on delivered-equipment cost. Values are taken from Peters et al.[186]

Fixed capital investment (FCI)	Percentage of Purchased Equipment
Purchased equipment (delivered, E)	100%
Installation	25-55%
Instrumentation (installed)	8-50%
Piping(installed)	16-68%
Electrical (installed)	15-30%
Building (including service)	5-68%
Yard improvement	10-20%
Service Facilities (installed)	30-80%
Engineering and supervision	32-33%

Construction expenses	34-41%
Legal expenses	4%
Contractor's fee	17-22%
Contingency	35-44%

Table A3. Typical percentage values for estimation total production cost. Values are taken from Peters et al.[186]

	Type of expenses	**Typical values**
Variable cost (some)	Labor supervision	15% of the labor cost
	Maintenance and repair	2-10% of fixed capital investment
	Operating supplies	15% of maintenance and repairs
	Laboratory charges	10-20% of the labor cost
	Royalties	0-6% of total production cost
Fixed cost (without depreciation)	Taxes (Property)	1-2% of fixed capital investment
	Financing	5-10% total borrowed capital
	Rent	8-12 percent of total rented property
	Insurance	1% of the fixed capital investment
Plant overhead cost	Plant overhead cost	50-70% of the total labor, supervision and maintenance cost
General expense	Administrative cost	15-25% of operating labor
	Distribution & marketing cost	2-20% of total product cost
	Research & development cost	5% of total product cost

	F1	**F2**	**G1**	**G2**
Reaction and preheating	2.20	4.13	3.17	3.85
Solvent evaporation	21.40	8.10	25.18	7.88
IL recovery	19.95	5.51	23.69	5.29
Condensing	40.66	13.33	48.06	12.88
Cooling	0.78	0.22	0.93	0.21
Total Energy (MJ/kg HMF)	84.99	31.29	101.03	30.10

7.3 Publications

Contents lists available at ScienceDirect

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Process integration for the conversion of glucose to 2,5-furandicarboxylic acid

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ABSTRACT

The development of biorefineries means that a key feedstock for many new processes will be sugars in various forms, such as glucose or fructose. From these feedstocks a range of chemicals can be synthesized using heterogeneous catalysis, immobilized enzymes, homogeneous catalysts, soluble enzymes, fermentations or combinations thereof. This presents a particularly interesting process integration challenge since the optimal conditions for each conversion step will be considerably different from each other. Furthermore, compared to oil-based refineries the feedstock represents a relatively high proportion of the final product value and therefore yield and selectivity in these steps are of crucial importance. In this paper using the conversion of glucose to 2,5-furandicarboxylic acid and associated products as an example, alternative routes will be compared with respect to achievable selectivity, and achievable yield.

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Keywords: Biorefineries; Glucose isomerase; 5-Hydroxymethylfurfural; 2,5-Furandicarboxylic acid

1. Introduction

While the increasing cost of oil is driving particular interest in the production of new fuels from biomass there is little doubt that today of equal importance is the production of chemicals from biomass. Indeed for the supply of fuels in the future there are many potential sources aside from biomass. In a world with limited (or very expensive) oil it is less clear where the chemicals of the future will originate. There is currently an existing infrastructure based on the use of the seven established platform chemicals (toluene; benzene; xylene; 1,3-butadiene; propylene; ethene; methane). In the short term one could consider if we can use the same infrastructure and just create the seven chemicals from alternative sources. However in the longer term it will be necessary to devise new processes based on a different set of platform chemicals. One group will be based around glucose (the hydrolytic product of starch and therefore readily available from biomass). In a biorefinery it will be necessary to develop a structure which can manage a range of feedstocks, a range of technologies and a range of products. This presents a considerable challenge for design and optimization as well as process integration. In order to illustrate the complexity and the challenge that lies ahead we have studied one specific example with a defined starting and endpoint: the production of 5-hydroxymethylfurfural (HMF) or 2,5-furandicarboxylic acid (FDA) from glucose or fructose. Greatest value is obtained by going the whole way from glucose to FDA. However even in this small reaction pathway there are many alternative technologies. Some can be integrated together, some give the required yield and selectivity, some are difficult to implement and others are untested at scale. This illustrates very well the challenge that design engineers face. To date glucose finds its major use in food applications (as a feedstock for sorbitol and high fructose corn syrup). The possibility of non-food products like HMF or FDA implies the use of other technologies not governed by the strict

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food regulations. Nevertheless all the potential technologies (whether approved for food or non-food production) need to be able to overcome the pH and temperature instability and limited solubility in organic solvents. It is because of the nature of glucose therefore that one obvious starting point is to use enzymatic catalysis (water based and under mild conditions). In this paper we will review the alternative technologies and routes from glucose to FDA, and discuss some of the limitations and challenges.

2. Biomass as a raw material for biorefineries

Nature is producing vast amounts of biomass driven by sunlight via photosynthesis:

$$nCO_2 + nH_2O \rightarrow (CH_2O)_n + nO_2$$

However, utilization of biomass for producing chemicals and fuels is still in its infancy with only 3.5% being used for food or non-food purposes. Plant biomass consists mainly of carbohydrates, lignin, protein and fats. Out of an estimated 170 billion metric tons of biomass produced every year roughly 75% are in the form of carbohydrates which makes biomass carbohydrates the most abundant renewable resource (Röper, 2002). Together with their amenability towards enzymatic processes this makes carbohydrates the center of attention when looking for new and greener feedstocks to replace petroleum for producing commodity chemicals as well as fuels. In plant biomass most of the carbohydrates are stored as sugar polymers such as starch, cellulose or hemicellulose.

Starch is the second largest biomass produced on earth and commonly found in vegetables, such as corn, wheat, rice, potatoes and beans. The total world production in 2004 was 60 million tons of which more than 70% came from corn. Starch consists of chains of glucose molecules, which are linked together by α-1,4 and α-1,6 glycosidic bonds. The two major parts of starch are amylose (20–30%), essentially linear α-1,4 glucan chains and amylopectin (70–80%), a branched molecule containing 4–5% α-1,6 linkages.

Starch is industrially hydrolyzed to glucose by the three enzymes: α-amylase, glucoamylase, and pullulanase (Schäfer et al., 2007). Bacterial α-amylases (EC 3.2.1.1) catalyze the hydrolysis of internal α-1,4 glycosidic bonds. This reduces the viscosity, which is necessary for further processing. Glucoamylase (EC 3.2.1.3) is an exo-amylase that is added to the partly hydrolyzed starch after liquefaction. Glucose units are removed in a stepwise manner from the non-reducing end of the molecule. The third enzyme is pullulanase (EC 3.2.1.41). Industrially used pullulanases are heat stable enzymes, which act simultaneously with glucoamaylase during saccharification. Pullulanases catalyze the hydrolysis of the α-1,6 linkages in amylopectin, and especially in partially hydrolysed amylopectin. Typical process conditions for production of glucose from starch are given in Table 1.

Cellulose is a glucose polymer consisting of linear chains of glucopyranose units linked together via β-1,4 glucosidic bonds. Unlike starch, cellulose is a crystalline material where inter- and intra-molecular hydrogen bonding gives rise to the very stable cellulose fiber. Hemicellulose is a polysaccharide consisting of short highly branched chains of different carbohydrate units, including five- as well as six-carbon units (e.g. xyloses, galactose, glucose, mannose and arabinose). Hemicelluloses are much easier to hydrolyze than cellulose. The structured portion of biomass, such as straw, corn stover, grasses and wood, is made of lignocellulose composed mainly of cellulose (30–60%), hemicellulose (20–40%) and lignin (10–30%). Both cellulose and hemicellulose consist of carbohydrate components whereas lignin is a highly branched aromatic polymer.

Currently, there is intensive research on the use of lignocellulosic raw material as a biomass source for producing chemicals and fuels (as exemplified by many of the other articles in this special edition). However this research still faces considerable challenges due to lignocellulose being remarkably resistant towards hydrolysis and enzymatic attack (Peters, 2007). Energy demanding thermal pre-treatment of lignocellulose is necessary in order to break up the extremely stable cellulose–hemicellulose–lignin composites prior to adding cellulose-hydrolyzing enzymes and the current situation does not allow the efficient use of lignocellulosic materials. Nevertheless, there is little doubt given the great abundance of lignocellulose that in the future this will become an attractive option. It is therefore important to continue to develop processes that can economically convert lignocellulose into chemicals. Moreover, glucose is one of the most abundant monosaccharides in biomass, accessible by enzymatic or chemical hydrolysis from starch, sugar or cellulose. Furthermore, a range of chemical products can be obtained from glucose which gives it a key position as a basic raw material/building block.

3. Glucose – a biorefinery building block

Fermentation of polymer building blocks is already under commercial introduction. For example, Cargill produces lactic acid by fermentation and products based on polylactic acid are being introduced to the market. Several companies focus on succinic acid as a polymer building block, but also as a potential raw material for chemicals (e.g. butanediol). 1,3-propandiol is marketed by DuPont Tate & Lyle BioProducts for Sorona™ polytrimethylene terephthalate (PTT) polyester. Likewise Cargill is working on developing 3-hydroxypropionic acid (3-HP). 3-HP is a potential raw material for existing chemicals such as propanediol and acrylic acid. Polyhydroxyalkanoate (PHA) is marketed by Telles, a J/V between ADM and Metabolix. Roquette, the French starch producer, has commercialized isosorbide, a derivative of sorbitol. Isosorbide is used as a co-monomer for high temperature polyethylene terephthalate. However, even if commercialization of polymer building blocks made by fermentation is commercially underway, the technology has certain drawbacks such as loss of carbon as CO_2, low yields and difficult recovery of the products

Table 1 – Process conditions for production of glucose from starch.

Process	Temperature (°C)	Dry substance content (%)	pH	Process time (h)
Jet cooking/dextrinization	105/95	30–35	5.2–5.6	0.1/1–2
Saccharification	60	30–35	4.3–4.5	25–50

from the fermentation broth. The technology presented here (combined chemical and enzymatic catalysis from glucose) has the potential to overcome these problems and represents a promising next generation technology.

One chemical transformation (besides fermentations) of carbohydrate monomers for the degradation of functionality is the dehydration reaction. This facilitates the removal of some of the functional groups in carbohydrates and allows the formation of defined building blocks. Triple dehydration of glucose yields HMF—a building block molecule that subsequently can be transformed into a multitude of bio-based chemicals. By a subsequent hydration reaction or an oxidation, HMF can be converted into levulininc acid or FDA, respectively. Both of these molecules are on the list of the 12 bio-based platform chemicals identified as being of highest potential to be converted into new families of useful molecules (Werpy and Petersen, 2004). In the following we will focus on the dehydration of glucose to HMF as an example of the need to efficiently combine enzymatic aqueous processes with inorganic heterogeneous catalytic processes that have so far mainly been developed for running reactions within the petrochemical industry.

HMF is in itself a rather unstable molecule. It can be found in natural products such as honey and a variety of heat processed food products formed in the thermal decomposition of carbohydrates. Interestingly, HMF can be chemically converted into a range of other valuable chemicals. The oxidation of HMF is of particular interest. Here, the ultimate objective is to obtain FDA as suggested by Schiwek et al. (1991). The diacid can be used as a replacement for terephthalic acid in the production of polyethylene terephthalate and polybutylene terephthalate (Gandini and Belgacem, 1997; Kunz, 1993) which was recently reviewed by Moreau et al. (2004). The partially oxidized compounds can also be used as polymer building blocks although these are more difficult to produce selectively. FDA is a chemically very stable compound. Its only current uses are in small amounts in fire foams and in medicine where it can be used to remove kidney stones.

Several extensive reviews describing the chemistry of HMF and its derivatives have been reported (see Fig. 1). The most recent review focuses on chemical transformation of biomass to a variety of chemicals with particular emphasis on the dehydration of monosaccharides giving either furfural (from pentoses) or HMF from hexoses, respectively (Corma et al., 2007). Moreau et al. (2004) described the recent catalytic advances in substituted furans from biomass and focused especially on the ensuing polymers and their properties. A review by Lewkowski (2001) on the chemistry of HMF and its derivatives also appeared recently. Two other relevant reviews are from Cottier and Descotes (1991) and Kuster (1990).

The mechanism for the dehydration of fructose to HMF has been interpreted to proceed via two different routes; either via acyclic compounds or cyclic compounds (Haworth and Jones, 1944; Kuster, 1990; Van Dam et al., 1986; Antal et al., 1990). Besides HMF, the acid-catalyzed dehydration can lead to several other by-products such as insoluble polymers, called humins or humic acids. In an industrial process it is very important to find the right process conditions that avoid the formation of humins as these, besides lowering the selectivity of the reaction, potentially can clog up your reactor or deactivate the heterogeneous catalysts.

In spite of all the research carried out within this area an efficient way of producing HMF or its corresponding dicarboxylic acid, FDA, still remains to be found. Traditionally, chemists have been struggling with finding an inexpensive way of producing pure HMF. Given the immense field of its application, it is interesting that relatively few of the listed reviews have described the challenges that might be faced in

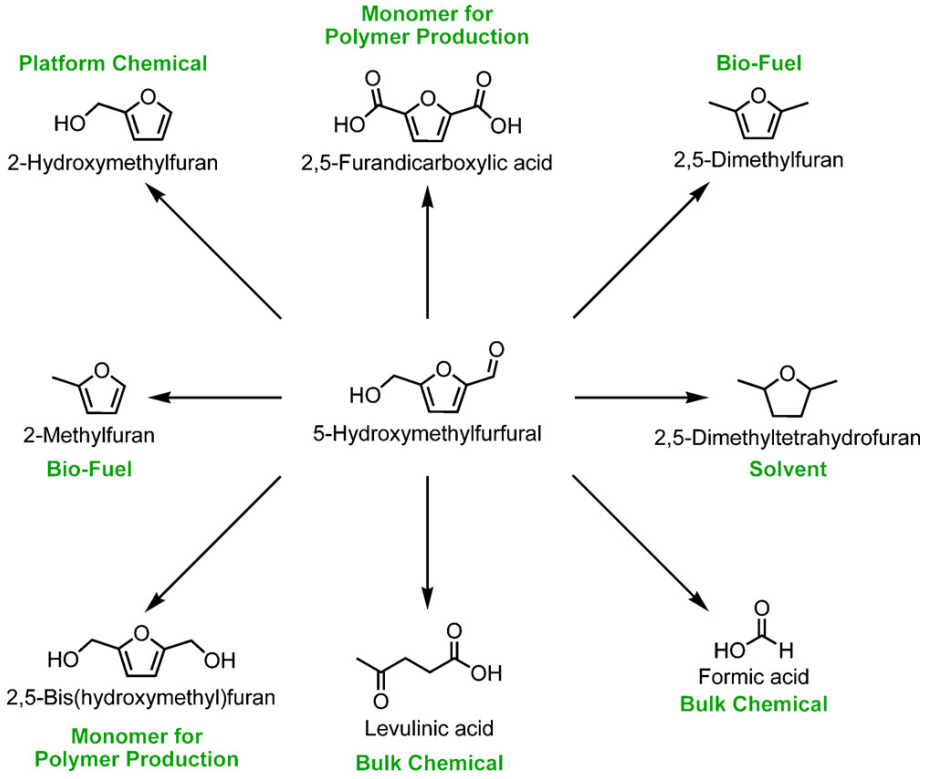

Fig. 1 – HMF as a precursor for a range of commercial chemicals.

Table 2 – Typical reaction conditions for immobilized glucose isomerase.

Process	Temperature (°C)	Dry substance content (%)	pH	Process time (h)
Isomerization	50–60	40–50	7–8	0.3–3

a biorefinery manufacturing HMF or its derivatives. The most likely biorefinery scenario will not be restricted to one product but make a series of high and low value products (including fuel). This allows the biorefinery to shift focus from one product to another if the market changes. In the case of HMF or FDA production this means that producing purely HMF or FDA is not the ultimate target and side-streams producing other valuable products besides HMF or FDA can actually be of benefit. One potential by-product of value is levulinic acid. This is formed via a rehydration of HMF to give levulininc acid along with formic acid. Both of these molecules are valuable products that are potentially worth isolating as side streams. In this respect the goal of completely selective dehydration may in the future be misplaced.

The synthesis of HMF is based on the acid-catalyzed triple dehydration of C6-sugar monomers, mainly glucose and fructose. However, various polysaccharides have also been reported as HMF sources (Rapp, 1987). The most convenient method for the preparation of HMF is by dehydration of fructose. When starting from ketohexoses (such as fructose) the dehydration reaction proceeds more efficiently and selectively. This can be explained by aldohexoses (such as glucose) only being able to enolyze to a low degree which is considered the limiting step in the production of HMF from glucose. However, glucose is the favored source of HMF due to the lower cost of glucose compared to fructose. Fructose may be obtained by enzyme or acid-catalyzed hydrolysis of sucrose and inulin or by the isomerization of glucose to fructose. Inulin is a linear β-2,1 linked fructose polymer which is terminated by a single glucose unit. It is found as a food reserve in a number of plants including Jerusalem artichoke and chicory. Industrially fructose is produced from glucose by the enzyme glucose isomerase (EC 5.3.1.5). The equilibrium conversion under industrial conditions is 50% making chromatographic separation necessary in order to obtain the industrial product of 55% fructose, which has sweetness similar to sucrose. Glucose isomerase is used industrially as an immobilized enzyme with typical reaction conditions as shown in Table 2.

Commercial immobilized glucose isomerase preparations used in a packed column have half-lives between 100 and 200 days. Most columns therefore last for more than 1 year and productivities are typically around 15 tons of syrup dry substance/kg immobilized enzyme.

4. Case studies

4.1. *Case 1: conversion of glucose/fructose to HMF*

To date most of the work regarding the acid-catalyzed conversion of fructose, and to a less extent glucose, into HMF has been carried out in aqueous reaction media. Obviously water being very abundant and non-hazardous is the preferred solvent of choice when exploring green and sustainable chemistry. Furthermore water is a good solvent for dissolving the monosaccharide substrates (fructose and glucose) as well as the product, HMF. However the dehydration of fructose to yield HMF in aqueous media is hampered by a competitive rehydration process resulting in the by-products levulinic acid and formic acid. In addition soluble and insoluble polymerization products (humins), that are thought to arise from the self- and cross-polymerization of HMF, fructose and other by-products seem to be more pronounced in an aqueous reaction medium than an organic one (Van Dam et al., 1986). Nevertheless, several interesting papers have been published on the dehydration of fructose into HMF. The conversion of glucose into HMF is more difficult and as a result there are only a few publications on this process.

4.1.1. *Aqueous media*

Several mineral acids such as HCl, H_2SO_4 and H_3PO_4 have been employed in the homogeneous catalyzed dehydration of fructose to yield HMF (Newth, 1951; Mednick, 1962; Román-Leshkov et al., 2006). So far, however, the yield and selectivity of reactions carried out in aqueous reaction media are not comparable to those observed in aprotic high-boiling organic solvents such as DMSO where the solvent also serves as the catalyst (Musau and Munavu, 1987). Despite high yields and selectivity, the cost of removing high-boiling solvents makes these solvents unsuitable for industrial and large-scale processes. Heterogeneous catalysts have, due to separation and recycling considerations, drawn more attention than homogenous catalysts. The use of various acidic heterogeneous catalysts such as niobic acid ($Nb_2O_5{\cdot}nH_2O$) and niobium phosphate ($NbOPO_4$) have been reported to have an intermediate selectivity of about 30% for the production of HMF at about 80% conversion of fructose (Carniti et al., 2006). Zirconium and titanium phosphates/pyrophosphates have been shown to have a very high selectivity of up to 100% at 100 °C in a period of 18 min for the formation of HMF in water. However as the reaction time increases, the selectivity drops fast which is thought to be due to the formation of polymeric by-products. Additionally, titanium oxides (TiO_2), zirconium oxides (ZrO_2) and H-form zeolites catalyze the dehydration reaction (Moreau et al., 1996). Especially interesting is the direct conversion of glucose to HMF which can be enhanced up to 5-fold compared to the hydrothermal dehydration, by employing an α-TiO_2 at 200 °C (Watanabe et al., 2005a,b). The main disadvantage with these catalysts seems to be the high temperature needed in order for the reaction to proceed without limited selectivity and conversion rates. Highly acidic cation-exchange resins such as those derivatized with sulfonic acid groups are also effective catalysts, providing the acidity of mineral acids together with the advantages of the heterogeneous catalysts (Rigal et al., 1981). These, often polystyrene based resins, can only tolerate temperatures up to around 130 °C, which reduces the range of their application. However this temperature range seems to be sufficient to overcome the activation energy barrier, when simultaneously applying the effect of microwave heating (Qi et al., 2008).

4.1.2. *Modified aqueous media and two-phase systems*

Phase modifiers have within the last couple of years proved very effective in promoting the conversion of fructose to HMF. Polar organic solvents that are miscible with water are added in order to increase the rate of the reaction to HMF and reduce the rate of the rehydration process forming by-products (Van

Dam et al., 1986). Commonly employed aqueous phase modifiers are acetone, DMSO and polyethylene glycol (PEG) (Qi et al., 2008; Chheda et al., 2007; Van Dam et al., 1986). A further modification of the aqueous phase system is the introduction of a second immiscible phase to create a two-phase reaction system. An organic phase extracts the HMF from the aqueous phase as it is produced and consequently reduces the formation of rehydration and polymeric by-products. Even with an initial concentration of fructose as high as 50 wt%, remarkable results with selectivity of 77% and a conversion of 90% at 180 °C with HCl as the catalyst have been reported. In comparison similar conditions in water resulted only in a selectivity of 28% and a conversion of 51% (Román-Leshkov et al., 2006).

4.1.3. *Non-aqueous organic solvents*

Until now, the best results for the dehydration of fructose to HMF have been made in high-boiling organic solvents. The low concentration of water prevents the rehydration of HMF to levulinic acid and formic acid. Iodine catalyzes the dehydration of the fructose part of sucrose in anhydrous DMF at 100 °C. Glucose is unaffected under the same conditions (Bonner et al., 1960). High selectivity has also been obtained when using PEG-600 as a solvent together with catalytic HCl. With the acid present a 1:1 solution of fructose and PEG-600 can be obtained at 85 °C (Kuster and Laurens, 1977). The first really high yields were reported by Nakamura and Morikawa (1980) using a strongly acidic ion-exchange resin as the catalyst in DMSO at 80 °C. These conditions gave a yield of 90% after 8 h. The rate of the reaction was strongly affected by the type of resin used (Nakamura and Morikawa, 1980). Quantitative yields, without the use of a catalyst, were reported soon after in DMSO at 100 °C for 16 h (Brown et al., 1982). Good results were also obtained during an investigation of the optimum fructose concentration in DMSO. With 8.5 molar equivalents of DMSO with respect to fructose, a yield of 92% was obtained at 150 °C without any catalyst after 2 h (Musau and Munavu, 1987).

None of the above examples are suitable for production on a large-scale. High-boiling aprotic solvents such as DMSO, DMF and NMP are all miscible with water as well as many other common organic solvents. This makes separation of the desired products very difficult. Furthermore, both DMF and NMP are considered to be teratogenic.

4.1.4. *Supercritical/subcritical solvents*

Since the best results for the dehydration of hexoses to HMF have been in high-boiling organic solvents, the use of low-boiling solvents in their sub- or supercritical state would be an interesting alternative. Subcritical water has emerged in recent years as a feasible alternative to organic solvents at larger scale. Its unique intrinsic acidic and basic properties, makes it particularly interesting as a reaction medium for the dehydration of carbohydrates. When glucose is dehydrated in pure subcritical water, HMF is formed with greater selectivity than when using sulfuric acid or sodium hydroxide as catalysts under the same pressures and temperatures (Simkovic et al., 1987). Watanabe et al. (2005a) explored the use of different TiO_2 and ZrO_2 catalysts in highly compressed water. The anatase-TiO_2 catalyst showed both basic and acidic properties and catalyzed the conversion of glucose to HMF. Yields were only about 20%, but the selectivity was more than 90%. The basic properties of the catalyst were thought to catalyze the isomerization of glucose to fructose, whereas the acidic properties were thought to catalyze the dehydration (Watanabe et al., 2005b). Yields of up to 50% were obtained when using fructose as the starting sugar and different zirconium phosphates as catalysts in subcritical water. No rehydration products were observed, yet the highest selectivity was not more than 61%. By-products were humins and furaldehyde (Asghari and Yoshida, 2006). Interesting results have recently been reported on the catalytic effect of H_3PO_4, H_2SO_4 and HCl in the direct conversion of glucose to HMF in water at 523 K. It was concluded that the weakest acid, H_3PO_4, was the best catalyst for the conversion of glucose into HMF and the strongest acid, HCl, was the best catalyst for the conversion of HMF to levulinic acid. The best yield for HMF was 40% (Takeuchi et al., 2008). More extensive studies on the kinetics of the dehydration of D-glucose and D-fructose in sub- and supercritical water have been made as well as the behavior of HMF under similar conditions (Kabyemela et al., 1999; Asghari and Yoshida, 2007; Chuntanapum et al., 2008).

Nevertheless, the overall results from sub- and supercritical water have so far been unsatisfactory in terms of yields. Bicker et al. (2003) explored other low-boiling solvents such as acetone, methanol and acetic acid. An acetone/water mixture at 180 °C and 20 MPa gave 99% conversion of fructose and a selectivity of 77% to HMF. This excellent result was explained by the structural similarities between acetone and DMSO, which would promote the furanoid form of fructose and hence favor the formation of HMF. The authors also propose a continuous process for the reaction (Bicker et al., 2003, 2005).

4.1.5. *Ionic liquids*

Another attractive alternative to high-boiling organic solvents is the use of ionic liquids. Their unique physical properties such as negligible vapor pressure and non-flammability make them particularly suitable as solvents for large-scale production. There is a possibility to design and functionalize the ions of the ionic liquid, giving them ability to work both as solvent and reagent for certain reactions. There are several examples of ionic liquids that have the ability to solubilize natural polymers such as cellulose, starch and chitin. This opens an excellent opportunity to convert crude biomass into fine chemicals (Liu et al., 2005; El Seoud et al., 2007).

The first dehydrations of fructose and glucose with the help of ionic liquids date back 25 years. Fructose was dehydrated in the presence of pyridinium chloride to HMF in high purity with 70% yield. The corresponding result for glucose was only 5% (Fayet and Gelas, 1983). In 1-butyl-3-methylimidazolium tetrafluoroborate and 1-butyl-3-methylimidazolium hexafluorophosphate, yields up to 80% from fructose were obtained using DMSO as a co-solvent and Amberlyst-15 resin as the catalyst. The DMSO helped to solubilize the starting fructose and the reaction was faster than in DMSO alone. Performing the reaction in 1-butyl-3-methylimidazolium tetrafluoroborate alone gave a yield of 50% within 3 h (Lansalot-Matras and Moreau, 2003). The best results so far from fructose were made by using the acidic 1-H-3-methylimidazolium chloride as reaction medium. This acted both as solvent and catalyst giving a yield of 92% after 15–45 min at 90 °C. There was no sign of HMF decomposition and glucose remained completely unreacted (Moreau et al., 2006). Recently remarkably good results were found using the ionic liquid 1-ethyl-3-methylimidazolium chloride together with $CrCl_2$, giving a total yield of 70% HMF directly from glucose and virtually no levulinic acid. The authors propose that the actual catalytic specie is the $CrCl_3^-$ ion formed together with the solvent

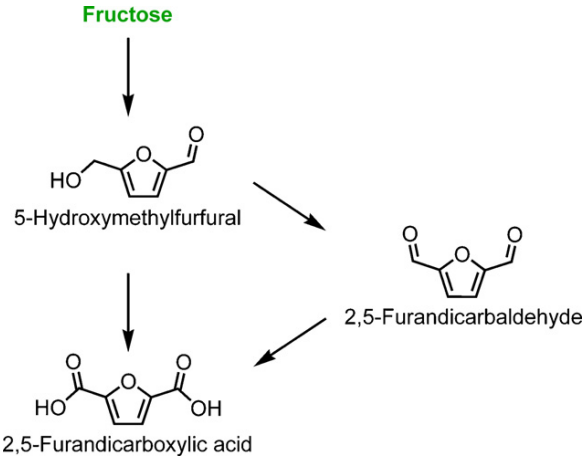

Fig. 2 – Oxidation of HMF to DFF and FDA.

and that it catalyzes the isomerization of β-glucopyranose to fructofuranose, which is subsequently dehydrated to HMF (Zhao et al., 2007). Bao et al. (2008) concluded that ionic liquids with a Lewis acid moiety were more efficient than those with a Brønsted acid counterpart when dehydrating fructose. These ionic liquids were also successfully immobilized on silica, giving a yield of up to 70% from fructose to HMF and completely retained their catalytic activity after five reaction cycles (Bao et al., 2008).

4.2. *Case 2: HMF oxidation to 2,5-diformylfuran and FDA*

FDA has been identified by the U.S. Department of Energy (DOE) biomass program as one of the 12 chemicals that in the future can be used as a feedstock from biomass in biorefineries (Werpy and Petersen, 2004). Due to the presence of the two carboxylic acid groups, FDA is considered to be a biorenewable building block to form polymers from biomass and therefore become an alternative to terephthalic, isophthalic and adipic acids, which are all produced from fossil fuels. Sugars in the form of mono- and disaccharides are easily available from biomass. The hexose type monosaccharides such as glucose and fructose can be catalytically dehydrated into HMF (Corma et al., 2007; Gallezot, 2007; Moreau et al., 2004). HMF can then be oxidized into FDA using a variety of routes and reaction types with stochiometric amount of oxidants. Most of them are described in a review by Lewkowski (2001), including electrochemical oxidation, use of barium and potassium permanganates, nitric acid and chromium trioxide. In this section we will focus on the recently reported catalytic routes for the oxidation of HMF into FDA.

4.2.1. *Oxidation of HMF to DFF*

Though production of FDA from HMF has been of great interest recently, there are few papers on catalytic aerobic oxidation of HMF. In the catalytic route to form FDA the partially oxidized intermediate 2,5-diformylfuran (DFF) is often observed (Fig. 2).

The dialdehyde is a useful product to form other derivatives, and a number of studies have reported on the selective formation of DFF. Thus, Halliday et al. (2003) reported oxidation of HMF to DFF using an in situ reaction protocol where HMF was directly generated from fructose and not isolated. Hence, using ion-exchange resins and, then, VOP-type catalysts the authors obtained DFF with a maximum yield of 45% based on fructose (Halliday et al., 2003). Carlini et al. (2005) reported that HMF, as a starting reagent or produced one pot from fructose, was oxidized to the corresponding dialdehyde in water with methylisobutylketone (MIBK), as well as pure organic solvents, with vanadyl phosphate (VPO) based catalysts (Zr, Nb, Cr, Fe modified) as such or using a TiO_2 support at 75–200 °C and 1 MPa. However, the reported yields were low (H_20:MIBK = 0:30–5:30, HMF conversion 3–10%, selectivity to DFF 100–60%, respectively). Considering the oxidation as a stand-alone reaction and changing the solvents to less polar ones (benzene, toluene) better conversion rates and selectivity were obtained, and using MIBK as a solvent lead to 98% conversion with 50% selectivity. However, in DMF the results are even better (at 150 °C) giving 84% conversion and 97% selectivity.

4.2.2. *Oxidation of HMF to FDA*

The above-described DFF may either be used as a valuable by-product or as an intermediate for obtaining FDA. On the other hand, catalytic reactions leading to the formation of FDA are also reported.

Partenheimer and Grushin (2000) obtained DFF from HMF using metal bromide catalysts (Co/Mn/Zr/Br). The reactions were carried out in acetic acid at atmospheric pressure and also at 70 bar; the yields were 57% and 63% with the conversion of HMF 98% and 92%, respectively. Cobalt as a catalyst was also used by Ribeiro and Schuchardt (2003). Using cobalt acetylacetonate as a bi-functional acidic and redox catalyst encapsulated in silica in an autoclave at 160 °C, they obtained FDA, from fructose via HMF formation, with 99% selectivity to FDA at 72% conversion of fructose. By in situ oxidation of HMF to FDA starting from fructose, Kröger et al. (2000) described a way of producing FDA via acid-catalyzed formation and subsequent oxidation of HMF in a MIBK/water mixture using solid acids for fructose transformation and PtBi-catalyst encapsulated in silicone and swollen in MIBK. The reaction was carried out in a reactor divided with a PTFE-membrane in order to prevent the oxidation of fructose. However, though in principle the integration process has been described, the yields remain quite low. The resulting yield of FDA was 25% based on fructose. In the oxidation of HMF to FDA the use of noble metals was first studied by Vinke et al. (1991). Here, mainly Pd, Pt, Ru supported on different carriers were used as the aerobic oxidation catalysts. Although all the noble metals revealed catalytic activities, only Pt supported on Al_2O_3 remained stable and active and gave quantitative yields of FDA. The reactions were carried out in water at pH 9 using a reaction temperature of 60 °C and a partial oxygen pressure of 0.2.

4.2.3. *Oxidation of HMF to FDA derivatives*

A new approach to the oxidation of HMF has been reported recently by Taarning et al. (2008) using methanol as both solvent and reagent. They performed a reaction with a gold nanoparticle catalyst in an autoclave at 130 °C and 4 bars of dioxygen, and obtaining FDA with 98% yield (according to GC analysis) and 60% isolated yield after sublimation.

5. Process technology

Table 3 indicates some of the key features of possible routes for the conversion of fructose to HMF. A number of observations can be made:

Table 3 – Key features of possible routes for the conversion of fructose to HMF.

Mode of operation[a]	Catalyst[b]	Temp.	Fructose concentration	Solvent media[c]	Highest yield	Reference
B	Hetero.	80 °C	3–4% (w/w)	Water, MIBK	41%	Carlini et al. (2005)
B	Homo.	170 °C	10% (w/w)	Water, DMSO, MIBK, 2-butanol, DCM	87%	Chheda et al. (2007)
B	Homo.	90 °C	3–50% (w/w)	$HMIM^+Cl^-$	92%	Moreau et al. (2006)
B	Hetero.	165 °C	10% (w/w)	Water, MIBK	69%	Moreau et al. (1996)
B	Hetero.	80 °C	6% (w/w)	Water	42%	Carlini et al. (2004)
			3% (w/w)		59%	
B	Homo.	180 °C	30% (w/w)	Water, DMSO, PVP, MIBK, 2-butanol	76%	Román-Leshkov et al. (2006)
			50% (w/w)		71%	
B	Hetero.	90 °C	10% (w/w)	Water, DMSO, PVP, MIBK, 2-butanol	59%	Román-Leshkov et al. (2006)
			30% (w/w)		54%	
B	Hetero.	110 °C	6–10% (w/w)	Water	31%	Carlini et al. (1999)
B		100 °C	6–10% (w/w)	Water, MIBK	74%	
C		85 °C	10–20% (w/w)	Water	26%	
B	Hetero.	100 °C	6% (w/w)	Water	85%	Benvenuti et al. (2000)
C	Hetero.	165 °C	0.5–3.5% (w/w)	Water, MIBK	–	Rivalier et al. (1995)

[a] Process is continuous (C) or batch (B).
[b] Catalyst is homogenous (homo.) or heterogenous (hetero.).
[c] Solent media are: methylisobutylketone (MIBK), dimethyl sulfoxide (DMSO), poly(1-vinyl-2-pyrrolidinone) (PVP), dicholormethane (DCM), and 1-H-3-methyl imidazolium chloride ($HMIM^+Cl^-$).

- Catalyst type
  A variety of catalysts like mineral and organic acids, salts, and solid acid catalysts such as ion-exchange resins and zeolites have been used in the dehydration reaction. The homogeneous acid-catalyzed processes are frequently associated with low selectivity (30–50%) for HMF at a relatively high conversion (50–70%) (Carlini et al., 1999). Moreover, problems related to separation and recycling of the mineral acid as well as of plant corrosion are expected. Thus, recent research has been based on heterogeneous acid catalysts which have considerable potential for industrial application (Carlini et al., 1999).
- Mode of operation
  The dehydration process has mostly been studied in batch operated reactors. Few researchers have examined a continuous process. One exception is the work reported by Kuster and Laurens (1977), who developed a continuous homogeneous catalyzed process for dehydration of fructose to HMF by using a tube reactor with polyethyleneglycol-600 as the solvent. Dehydration of fructose in a continuous stirred tank reactor with phosphoric acid and MIBK as a solvent was also reported by Kuster and van der Steen (1977).
- Media
  The dehydration of hexoses and pentoses has been studied in water, organic solvents, biphasic systems, ionic liquids, and near- and supercritical water. The most convenient solvent for dehydration of fructose to HMF is water. However, water is the reactant in the reverse reaction. Moreover, with the presence of water, HMF decomposes to levulinic acid, formic acid and humins. Organic solvents are thus introduced to improve the dehydration reaction by shifting the equilibrium and suppressing HMF hydrolysis. Relatively high yields were reported for the use of DMSO with ion-exchange catalysts (Nakamura and Morikawa, 1980; Rigal and Gaset, 1985) and quantitative yields of HMF were also reported by heating fructose in the absence of catalyst (Brown et al., 1982; Musau and Munavu, 1987). In spite of the advantages of using DMSO, the difficulties of separation limit its application. Moreover, possible toxic sulfur containing by-products from decomposition of DMSO may cause a risk to health and the environment (Moreau et al., 2004). A biphasic reactor system has been developed to suppress HMF degradation by using organic solvent to separate HMF immediately from the reaction medium as it forms. Consequently some work has been carried out to find the proper extraction solvent. Amongst the solvents reported, MIBK is the most commonly used solvent for extraction of HMF. Due to its relatively low-boiling point, it is relatively easy to separate HMF from MIBK. In general, poor HMF partitioning in the organic solvents leads to the use of large amounts of solvent. Purification of the diluted HMF product thus causes large energy expenditure in the subsequent process (Chheda et al., 2007).

5.1. *New technology*

Román-Leshkov et al. (2006) developed a cost-effective method to produce HMF using a biphasic batch reactor system with phase modifiers. They obtained D-fructose to HMF in high yields (>80%) at high fructose concentrations (10–50 wt%) and delivered the product in a separation-friendly solvent. In the biphasic reactor system, DMSO and/or poly(1-vinyl-2-pyrrolidinone) (PVP) were added as modifiers to suppress the formation of dehydration by-products in the aqueous phase with HCl as the acid catalyst. The product was continuously extracted into an organic phase MIBK modified with 2-butanol to enhance partitioning from the reactive aqueous solution. In this study, they reported an improvement in selectivity from 60 to 75% by adding small amounts of aqueous phase modifiers (such as DMSO and PVP) in the biphasic reactor system. Additionally, by optimizing the partitioning of HMF product into the organic phase, the process not only minimized the degradation of HMF in the aqueous phase, but also achieved efficient product recovery.

Zhao et al. (2007) used a metal chloride catalyst in an ionic liquid for the dehydration of HMF. In this reaction, the only water present in the system was from the dehydration of fructose to HMF reaction, which indicated that the conditions for HMF degradation to levulinic and formic acids were not met. By using this metal chloride in ionic liquid, the reaction could take place at reduced temperature, 80 °C for fructose dehy-

dration, and 100 °C for glucose. 90% yield was achieved from fructose and 70% yield from glucose.

Bicker et al. (2003) reported the use of benign solvents such as acetone, methanol or acetic acid in a sustainable process outline. They reported the dehydration of D-fructose to HMF in sub- and supercritical acetone/water mixtures. The use of this reaction media resulted in higher yields of HMF (77% selectivity, 99% conversion). No solid impurities (humins) were formed. The authors also claimed the potential for a technical process based on this low-boiling point solvent, whereby a price for HMF of about 2 Euro/kg could be achieved if fructose was available at a price of around 0.5 Euro/kg.

However all these new technology approaches for making HMF from fructose have been carried out at a small scale. On a larger scale Rapp has reported yields of ~2.5 kg HMF from aqueous dehydration of fructose (Rapp, 1987). The production of HMF, close to a kg scale, has also been reported using DMSO as the reaction media (M'Bazoa et al., 1990). Nevertheless since high selectivity is crucial for implementing this reaction on an industrial scale, the recent research has been highly focused on alternative routes for improving the selectivity of the dehydration reaction.

5.2. *Process implementation, integration and scale-up*

In order to comply with the demands of efficient and specific conversions of the chemical reactants in a biorefinery with a minimum of economic cost, a special focus on process implementation, integration and scale-up must be paid. The development of combined biological and chemical catalytic reactions without intermediate recovery steps has the potential to become an important future direction for carrying out sustainable organic syntheses (Hailes et al., 2007).

The synthesis of a variety of important chemical building blocks involves multistep reactions often catalyzed by a chemical or biological catalyst. In many cases, the optimal operating conditions are rather different for the individual steps of such synthesis reactions. However, it could prove favorable if such reaction steps are combined or integrated, allowing them to occur concurrently, in proximity to one another, and at or close to their respective optimal operating conditions. Also from an engineering point of view, integration of unit operations could contribute to among other things simpler design, less equipment and less piping (Koolen, 1998). Furthermore, integration could reduce operating time and costs as well as consumption of chemicals and use of energy (Bruggink et al., 2003). An important aspect of process integration is the different working condition for the individual reactions. When the aim is to match different reactions involving enzymes, important factors such as enzyme stabilities, reaction rates, reaction media (e.g. pH, temperature, pressure) and reactor design must be considered. Tools to aid integration of different processes include reactor compartmentalization (Fournier et al., 1996; Byers et al., 1993; de Jong et al., 2008; Chen et al., 1997), medium engineering (Bao et al., 2008; Zhao et al., 2007), ISPR (Freeman et al., 1993; Woodley et al., 2008), optimized reactor designs (Stankiewicz and Moulijn, 2003) and multifunctional catalysts (Bruggink et al., 2003).

The conversion of glucose to FDA involves three steps, each with different optimal physical and chemical parameters like pH, temperature and pressure. Furthermore, the catalysts are of different nature with a bio-catalyst (enzyme) in the isomerization of glucose to fructose and a number of potential chemical catalysts of both heterogeneous and homogeneous nature in the following dehydration and oxidation reactions. While the potential for integration exists, it is only via an economic evaluation that such options can be further considered. A valuable process implementation tool to achieve both qualitative and quantitative understanding of the reaction processes and their potential for improvement is mathematical modeling. A good model should facilitate knowledge and understanding of the chemical reactions and include in a quantitative manner the most important physical and chemical governing parameters. As more is understood about the alternative synthetic routes to FDA, the appropriate modeling tools will also need to be developed.

6. Future outlook

With the implementation of biorefineries and increased interest in biofuel it is clear that the associated sugar-based chemistry will provide a rich variety of chemical products as building blocks for higher value molecules. The extent to which this happens depends on two factors. First the economics of the biorefinery will act as a driver in many cases to provide a means to develop higher value products alongside fuel. Ultimately the value of each product tree will need to be evaluated alongside the associated cost of implementing additional technology. Secondly it is clear that new technology and improved catalytic methods are required to produce high value building blocks such as FDA. Some of the more promising routes lie in new media such as ionic liquids but it is also clear that far higher selectivities are required. In this respect enzyme based catalysis will have a particular and likely expanding role in the future development of biorefinery technology. Finally, the implementation of new technology for biorefineries must be evaluated within the context of green chemistry and the necessary environmental requirements. For example the selection of organic solvents and catalysts must adhere to the criteria for sustainable processing. This is essential in order to ensure that new processes use sustainable processing methods as well as making use of sustainable resources.

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Direct conversion of glucose to 5-(hydroxymethyl)furfural in ionic liquids with lanthanide catalysts

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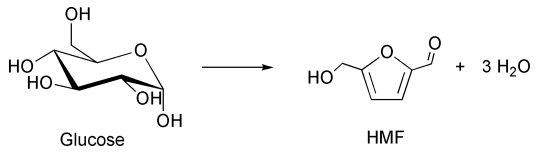
The direct conversion of glucose to 5-(hydroxymethyl)furfural (HMF) in ionic liquids with lanthanide catalysts was examined in search of a possibly more environmentally feasible process not involving chromium. The highest HMF yield was obtained with ytterbium chloride or triflate together with alkylimidazolium chlorides. Notably, a higher reactivity was observed when the hydrophobicity of the imidazolium cation was increased, in contrast to analogous chromium catalyst systems. This indicates a different reaction mechanism for the lanthanides than for the chromium catalyst systems.

Introduction

In recent years, the search for alternatives to today's platform chemicals derived from fossil sources has intensified. One molecule under particular scrutiny has been 5-(hydroxymethyl)furfural (HMF), which is expected to become an important precursor to fuels, solvents and polymers in the chemical infrastructure.[1-3]

HMF is formed by dehydration of hexoses under elevated temperature (Scheme 1, exemplified for glucose). The mechanism of the dehydration of hexoses has been subject of some debate, and proposals include both a mechanism consisting of only cyclic intermediates[4-8] as well as an open-chain mechanism.[9-13]



Scheme 1 Dehydration of glucose to HMF.

The dehydration of fructose is quite facile – even in the absence of catalyst – in high-boiling solvents such as DMSO, DMF and DMA,[14,15] whereas glucose requires a special catalyst for the formation of HMF.[16-19] However, fructose is derived from glucose in a process that only yields about 50% of fructose and involves a chromatographic step in order to be purified.[20] Consequently, in order to find an economical and environmentally feasible industrial process for the production of HMF, an efficient direct conversion from glucose would be most beneficial.

In the last five years or so, interesting results have been presented on the dehydration of hexoses by the use of ionic liquids. As in the case of high-boiling organic solvents, ionic liquids have proven to be efficient media for converting fructose to HMF.[21-25] More importantly, very good results have been shown for the direct conversion of glucose to HMF (up to 70% yield) in 1-ethyl-3-methylimidazolium chloride ([EMIm]Cl) with a catalytic amount of chromium(II) chloride.[16] In the proposed mechanism, a complex between ionic liquid and $CrCl_2$ interacts with the open chain of glucose, leading both to isomerization to fructose and direct conversion to HMF (Scheme 2).

An even higher yield of HMF was obtained when using chromium(II) or chromium(III) chloride complexed with sterically hindered carbenes.[17] Comparable yields were also shown using a large surplus of metal halides in DMA together with chromium(II/III) chloride.[18] Here a detailed mechanism of the actual role of the halide in the dehydration was also proposed. In this mechanism, fructose initially loses one water molecule, and the nucleophilic halide is then added to the anomeric carbon. The intermediate formed is then deprotonated to an enolic species, which is subsequently dehydrated twice to form HMF. Alternatively, the halide acts as a base in the second step and generates the enolic intermediate by deprotonation (Scheme 3).

Apart from chromium chloride, there are no reports of equally efficient catalysts for the direct conversion of glucose to HMF. A very recent publication showed, however, that a dual-function catalyst composed of sulfated zirconia on alumina support could convert glucose directly to HMF with a moderate yield, presumably *via* glucose isomerization to fructose followed by dehydration.[19] Furthermore, lanthanide chlorides have been shown to have a catalytic effect on glucose dehydration in supercritical water.[26] Notably, no leuvulinic acid or formic acid was observed here, as is normally the case when exposing HMF to aqueous acidic conditions.[27] In the study, kinetic and spectroscopic experiments suggested weak interaction between lanthanide and saccharide, resulting in higher reaction rates for smaller, less hydrated and heavier lanthanide ions.[28,29]

Our objective in this work was to combine in particular the heavier lanthanide catalysts with ionic liquids and to investigate its catalytic effect on the direct conversion of glucose to HMF. Thus, imidazolium-based ionic liquids were used as solvents together with various lanthanide chloride catalysts in

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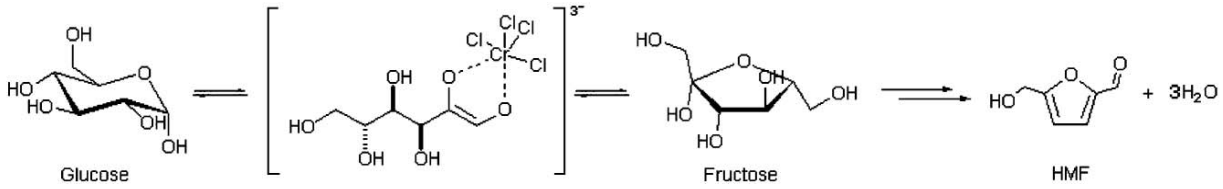
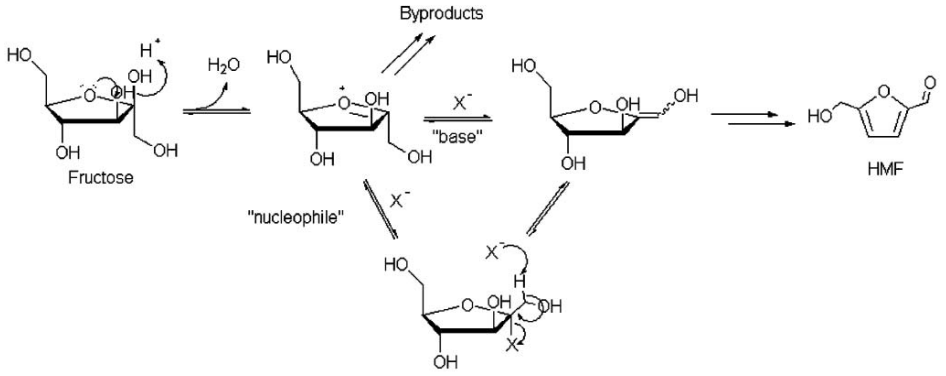


Scheme 2 Possible mechanism for the chromium-catalyzed dehydration of glucose to HMF in ionic liquids.[16]



Scheme 3 Proposed mechanism for the dehydration of fructose to HMF with halides.[18]

Table 1 HMF degradation in ionic liquids[a]

Ionic liquid	Conversion of HMF (%)
[MIm]Cl	9
[EMIm]Cl	3
[BMIm]Cl	29
[HMIm]Cl	9
[OMIm]Cl	11
[EMIm]OAc	> 99
[BMIm]OAc	> 99
[Choline][dmp][b]	6
[MIm][HSO_4]	69
[EMIm][$N(CN)_2$]	59
[EMIm][$C_2H_5OSO_3$]	9
[EMIm][$AlCl_4$]	77

[a] *Reaction conditions*: 1.0 g ionic liquid, 100 mg (0.56 mmol) glucose, 100 °C, 8 h. [b] dmp = dimethyl phosphate.

the temperature range 120–200 °C. Additionally, the investigation was expanded to include even stronger Lewis acids such as ytterbium triflate.

Results and discussion

We initially screened the stability of HMF in several ionic liquids at elevated temperature to make sure that the ionic liquid used was not detrimental to the desired product. As seen from the data in Table 1, all ionic liquids induced some degradation of HMF during the stability tests. The acidic and basic ionic liquids proved to promote highest degree of degradation, whereas the imidazolium chlorides, [EMIm][$C_2H_5OSO_3$] and [Choline][dmp] were the most benign.

On the basis of the initial experiments, we further discovered that there was no HMF formed from glucose in ionic liquids that did not have chloride or other halides as anion. This is in agreement with the mechanism proposed by Binder and Raines,[18] where the chloride acts as a nucleophile and promotes the dehydration of the furanose fructose. Consequently, our study focused on the alkylimidazolium chlorides as solvents. [BMIm]Cl or [EMIm]Cl converted only fructose to HMF without additives (as also reported by Zhao *et al.*[16]) and not glucose. The addition of lanthanide chlorides, on the other hand, revealed a catalytic effect on glucose conversion (but not on fructose conversion), even though temperatures above 140 °C were required to avoid slow reactions and negligible yields. Furthermore, methylimidazolium chloride, which previously has given an excellent conversion of fructose to HMF,[23] gave less than one percent HMF from glucose with any lanthanide.

In the experiments with lanthanides (Table 2), cerium had very little catalytic effect in both [BMIm]Cl and [EMIm]Cl, whereas the other lanthanides showed quite different behaviours depending on the liquid. In the case of [EMIm]Cl, the reactivity for the lanthanide chlorides was the highest for promethium and then decreased almost linearly through the heavy lanthanides to $YbCl_3$. Moreover, when using the more Lewis-acidic ytterbium

Table 2 Lanthanide-catalyzed dehydration of glucose in [EMIm]Cl and [BMIm]Cl[a]

	[EMIm]Cl		[BMIm]Cl	
Catalyst	Yield (%)	Selectivity (%)	Yield (%)	Selectivity (%)
$CeCl_3$	3	3	3	4
$PrCl_3$	13	27	7	22
$NdCl_3$	12	24	8	23
$DyCl_3$	10	19	10	23
$YbCl_3$	5	7	12	15
$Yb(OTf)_3$	10	16	24	37

[a] *Reaction conditions*: 1.0 g ionic liquid, 100 mg (0.56 mmol) glucose, 0.056 mmol catalyst, 140 °C, 6 h.

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triflate, a comparable yield to that of dysprosium chloride was obtained.

In [BMIm]Cl a completely different pattern was observed. Here the yield increased gradually from $CeCl_3$ to $YbCl_3$. This is consistent with the earlier relative catalytic effect found in supercritical water.[26,28,29] Furthermore, ytterbium chloride and ytterbium triflate gave significantly higher yields in [BMIm]Cl than in [EMIm]Cl. This is the opposite of what has been shown earlier using chromium catalysts, where the yields were markedly better in [EMIm]Cl,[16] thus clearly suggesting different catalyst–ionic liquid interaction in the systems.

Increasing the catalyst concentration of $YbCl_3$ in [EMIm]Cl, up to as much as 30 mol%, did not reveal any improvement in HMF yield. In contrast, the amount of catalyst had a significant effect on the HMF yield in [BMIm]Cl, thus further signifying differences between the catalytic systems (Fig. 1).

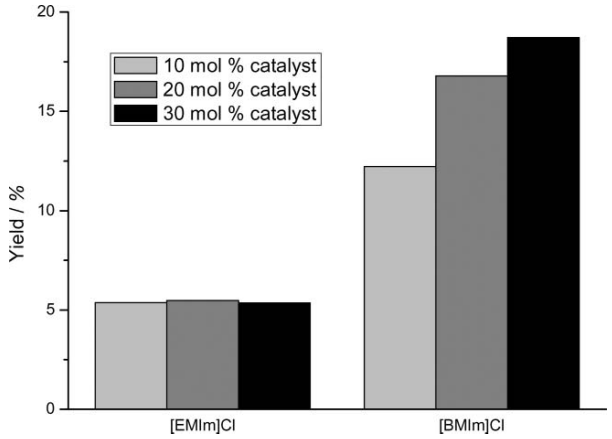

Fig. 1 Dehydration of glucose in [EMIm]Cl and [BMIm]Cl at 140 °C for 6 h with different amount of $YbCl_3$ catalyst. The reaction contained 1.0 g ionic liquid, 100 mg (0.56 mmol) glucose and 16 mg (0.056 mmol), 32 mg (0.112 mmol) and 48 mg (0.168 mmol) $YbCl_3$, respectively.

During dehydration in [BMIm]Cl, the selectivity towards HMF reached a maximum already after 10 min and a maximum yield after 30 min. The HMF was then slowly degraded due to the high temperature (Fig. 2). At an even higher temperature of 200 °C the yield was slightly increased, but at the expense of an even faster degradation of the product. In this case maximum yield was obtained after five minutes, and HMF was completely degraded after two hours (Fig. 3). All reactions formed substantial amounts of humins, but no other by-products were detected, as the essential anhydrous conditions (small amount of water is formed upon dehydration) prevented rehydration of HMF into leuvulinic acid and formic acid.

When it comes to finding an explanation why a longer alkyl chain on the imidazolium ring gave higher reaction rates for $YbCl_3$ and $Yb(OTf)_3$ catalysts, a possible reason could be related to ion pairing in the solvent. Cations with more hydrophobic character would be expected to have a weaker association with the chloride ion, which in turn would become more reactive. Earlier work has already shown that rates of reactions in ionic liquids involving halides are highly dependent on the nature of the cation.[30] This was also one of the rationales in the work of

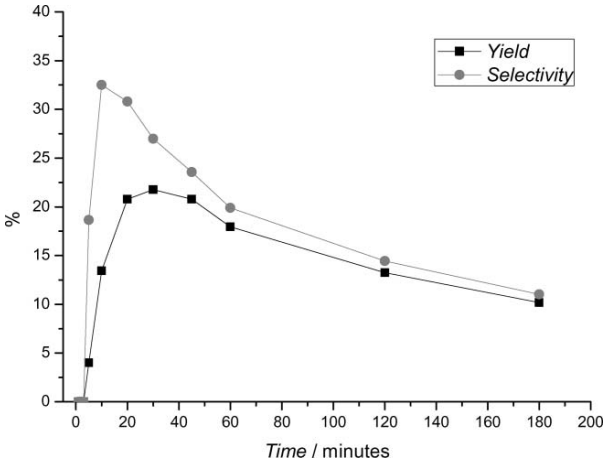

Fig. 2 Dehydration of glucose in [BMIm]Cl catalyzed by $YbCl_3$ at 160 °C as a function of the reaction time. The reaction contained 1.0 g ionic liquid, 100 mg (0.56 mmol) glucose and 16 mg (0.056 mmol) $YbCl_3$.

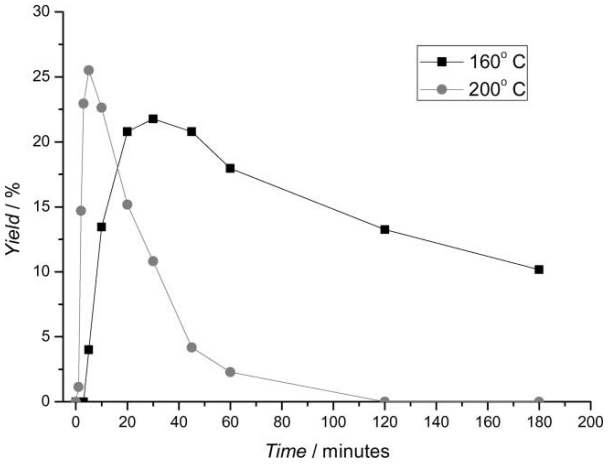

Fig. 3 Dehydration of glucose in [BMIm]Cl catalyzed by $YbCl_3$ at 160 °C and 200 °C as a function of time. Both reactions contained 1.0 g ionic liquid, 100 mg (0.56 mmol) glucose and 16 mg (0.056 mmol) $YbCl_3$.

Binder and Raines,[18] who combined LiCl with DMA in order to produce weakly ion-paired chloride ions for sugar dehydration. In order to examine the effect of ion-pairing more closely, additional experiments with even longer alkyl chains, such as 1-hexyl-3-methylimidazolium chloride ([HMIm]Cl) and 1-octyl-3-methylimidazolium chloride ([OMIm]Cl), were performed. In these experiments, a faster conversion and a small increase in yield could actually be seen when using [HMIm]Cl or [OMIm]Cl as solvents (Fig. 4), even though it was less pronounced than the difference between [EMIm]Cl and [BMIm]Cl. The decrease in selectivity for [HMIm]Cl and [OMIm]Cl compared to [BMIm]Cl could be a result of the faster formation of humins.

Conclusions

We have shown that lanthanides catalyze the conversion of glucose to HMF in dialkylimidazolium chlorides. The strongest Lewis acids, $YbCl_3$ and $Yb(OTf)_3$, gave the highest yields, even

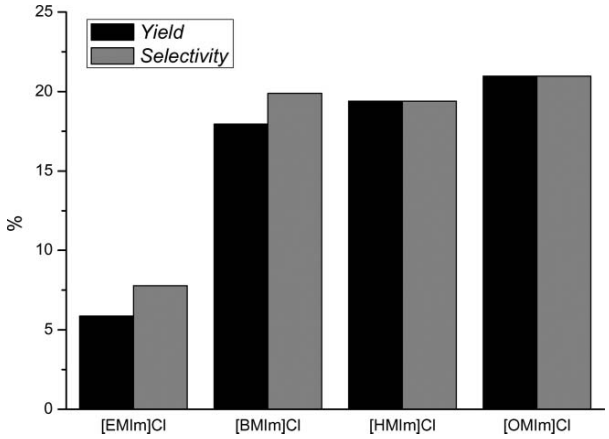

Fig. 4 Dehydration of glucose in [EMIm]Cl, [BMIm]Cl, [HMIm]Cl and [OMIm]Cl at 160 °C for 1 h. All reactions contained 1.0 g ionic liquid, 100 mg (0.56 mmol) glucose and 16 mg (0.056 mmol) $YbCl_3$.

though these were moderate (24%) compared to $CrCl_2$ (70%).[16] Our results also suggest that the mechanism of the reaction might be different to that of chromium-catalyzed dehydration of glucose.

In the chromium system, highest yields are obtained with [EMIm]Cl, whereas the yield decreases with more hydrophobic imidazolium cations.[16] In this reaction, chromium(II) chloride is believed to form a complex with the ionic liquid and then associate with the open chain form of glucose.[16] Ytterbium showed a different reaction pattern, whereby the yield increased as the hydrophobic character of the imidazolium ring increased. We believe that the increase in reaction rates are due to weaker ion pairing between the chloride and imidazolium cation, making this more reactive in the dehydration mechanism. Furthermore, ytterbium could be less prone to form complexes with the imidazolium chlorides, which would explain the difference in reactivity compared to chromium.

Further studies on the actual complexation between lanthanide chlorides and imidazolium chlorides are needed to clarify the exact reaction pattern with glucose. Modeling of the various structures and intermediates together with the metals could also give new insights into the mechanism. Combined, this information could provide valuable directions on how to improve the lanthanide–ionic liquid systems to become competitive with present chromium systems.

Experimental

Materials and apparatus

Glucose (99.5%), 1-hexyl-3-methylimidazolium chloride (98%), 1-octyl-3-methylimidazolium chloride (98%) and ytterbium triflate (99%) were purchased from Aldrich. [EMIm][$N(CN)_2$] (98%), [Choline][dmp] (98%) and [EMIm][$C_2H_5OSO_3$] (98%) were purchased from Solvent Innovation. All other ionic liquids were obtained from BASF (>95%). Lanthanide chlorides (p.a.) were purchased from Rare Earth Ltd. All experiments were performed under nitrogen atmosphere using a Radley Carousel 12 Plus Basic System.

Dehydration reactions

A 40 mL reaction tube was charged with ionic liquid (1 g) and lanthanide(III) chloride (0.056 mmol) and heated at 100 °C for 1 h. Glucose (100 mg, 0.56 mmol) was then added and the solution stirred for 3 h at 140 °C. After reaction the reaction tube was cooled in an ice bath and water (5 mL) added. The solids were filtered off and the filtrate analyzed by HPLC (Agilent 1200 series, Bio-Rad Aminex HPX-87H, 300 mm × 7.8 mm pre-packed column, 0.005 M H_2SO_4 mobile phase, 60 °C, 0.6 mL min^{-1}).

Definitions of yield and selectivity

The yields and selectivities were based on conversion of glucose and confirmed by calibration of standard solutions of the products and reactants involved. With a known molar amount of all components, the conversion, yield and selectivity were calculated from the equations below:

$$\text{Glucose conversion} = \left(1 - \frac{\text{Amount of glucose}}{\text{Starting amount of glucose}}\right) \times 100\% \quad (1)$$

$$\text{Yield of HMF} = \frac{\text{Amount of HMF}}{\text{Starting amount of glucose}} \times 100\% \quad (2)$$

$$\text{Selectivity of HMF} = \frac{\text{Yield of HMF}}{\text{Glucose conversion}} \times 100\% \quad (3)$$

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Metal-Free Dehydration of Glucose to 5-(Hydroxymethyl)furfural in Ionic Liquids with Boric Acid as a Promoter

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Abstract: The dehydration of glucose and other hexose carbohydrates to 5-(hydroxymethyl)furfural (HMF) was investigated in imidazolium-based ionic liquids with boric acid as a promoter. A yield of up to 42% from glucose and as much as 66% from sucrose was obtained. The yield of HMF decreased as the concentration of boric acid exceeded one equivalent, most likely as a consequence of stronger fructose–borate chelate complexes being formed. Computational modeling with DFT calculations confirmed that the formation of 1:1 glucose–borate complexes facilitated the conversion pathway from glucose to fructose. Deuterium-labeling studies elucidated that the isomerization proceeded via an ene–diol mechanism, which is different to that of the enzyme-catalyzed isomerization of glucose to fructose. The introduced non-metal system containing boric acid provides a new direction in the search for catalyst systems allowing efficient HMF formation from biorenewable sources.

Keywords: boric acid · catalysis · furfural · glucose · ionic liquids

Introduction

The impending exhaustion of fossil resources and climate change has prompted an intensified research for new and better pathways for chemicals and fuels from renewable sources. Particular attention has been set on 5-(hydroxymethyl)furfural (HMF), formed by the triple dehydration of hexoses, which is expected to play an important role in a future carbohydrate-based economy (Scheme 1).[1,2] HMF is primarily considered to be a starting material for its diacid counterpart (FDA) which is a possible replacement of terephthalic acid as a monomer in plastics.[3] Reduction of the furan ring would yield compounds suitable as solvents or fuels (Scheme 1).[4]

The formation of HMF from fructose is achieved readily at elevated temperatures in high-boiling molecular solvents or ionic liquids with or without an acid catalyst.[5–10] The most important industrial method for fructose production is by the enzymatic isomerization of glucose syrup, a process yielding only about 50% fructose.[11] Direct conversion of the obtained aqueous glucose/fructose mixture would be problematical since the dehydration in water suffers from side reactions by which HMF is rehydrated to leuvulinic acid and formic acid.[12] In order to find an economical and environmentally feasible industrial process for the production of HMF, an efficient direct conversion from glucose would therefore be most beneficial. Unlike the dehydration of fructose, however, the dehydration of glucose to HMF demands a special catalyst to attain acceptable yields. This has so far been achieved by lanthanide chlorides,[13] stannous chloride[14] and chromium chlorides,[15–18] with only the latter providing yields that could be adequate for a cost effective process development. The main difficulty in the dehydration is polymerization of the sugars during the reaction. The polymers formed, commonly known as humins, vary in size and are either soluble or insoluble in water depending on chain length.

In this work we have focused on finding an alternative to chromium chloride as catalyst for the direct dehydration of glucose to HMF. It is well known that carbohydrates form stable chelate complexes with boric acid[19–21] of the form shown in Scheme 2 and catalyze the isomerization of aldohexoses to ketohexoses in aqueous basic environment.[22,23]

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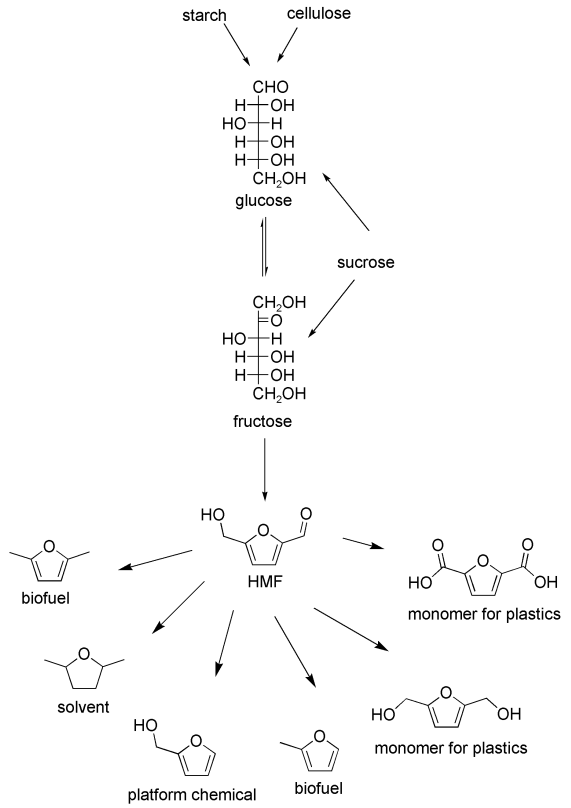
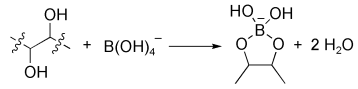


Scheme 1. Formation of HMF from hexoses and derivatization further to compounds with important applications in a post-petrochemical world, for example, solvents and fuel.



Scheme 2. Formation of boric acid–diol complex.

The ability to form stable complexes with fructose has further been utilized as a method of enriching fructose in the isomerization of glucose to fructose by the enzyme glucose isomerase.[24] Boric acid is also known to catalyze several reactions with important synthetic applications such as esterifications,[25] cyclization reactions[26] and decarboxylations.[27] So far no successful dehydrations of glucose to HMF with the aid of boric acid have been reported. With the assumption that the boric acid-sugar interaction also might stabilize intermediates or transition states in the isomerization of glucose to fructose or even the dehydration to HMF, we surmised that boric acid could act as a catalyst for the direct conversion of glucose to HMF in ionic liquids. Compared with the technologies developed up to now, this would be beneficial from both an environmental as well as an economical point of view, since boric acid is a non-toxic, nonmetal and inexpensive compound that exists in great abundance in nature, primarily as sodium borate.

In the work we demonstrate the effect of boric acid in the dehydration with different carbohydrates and bring clarity to the mechanism by the aid of computational modeling and experiments with deuterated glucose.

Results and Discussion

Dehydration of glucose: Based on the results from our previous work,[13] we focused on the glucose dehydration using alkylmethylimidazolium chlorides as the reaction media. To demonstrate the effect of the boric acid as a promoter we chose an initial catalyst load of 1.0 equivalent with respect to glucose in order to form a 1:1 sugar/boric acid complex. At a temperature of 120 °C the dehydration of glucose (10 wt %) in 1-ethyl-3-methylimidazolium chloride ([EMIm]Cl) and 1-butyl-3-methylimidazolium chloride ([BMIm]Cl) with boric acid showed that up to 40 % yield of HMF could be obtained (Figure 1). The yield was higher in [EMIm]Cl than in [BMIm]Cl as is the case with chromium catalysts.[15] The yield appeared to reach a maximum in both reactions after 3 h where after it slowly declined as a consequence of degradation or polymerization. In the case of [EMIm]Cl the highest HMF selectivity of approximately 50 % was reached after one hour of reaction. Full conversion was not reached until after 21 h. The maximum obtained HMF selectivity in [BMIm]Cl was of around 30 % which also coincided with the highest yield of around 20 % after 3 h. Close to full conversion in [BMIm]Cl was also reached after 21 h.

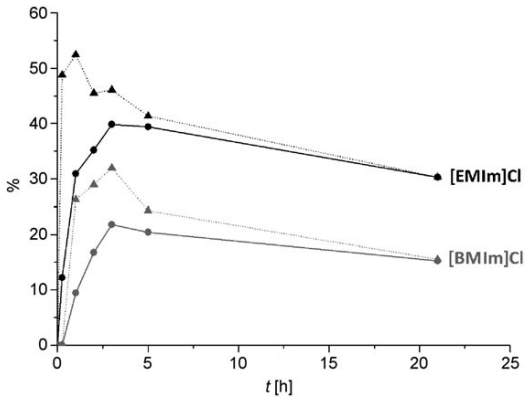


Figure 1. Dehydration of glucose in [EMIm]Cl at 120 °C. The reaction contained ionic liquid (1.0 g), glucose (100 mg, 0.56 mmol) and boric acid (34.3 mg, 0.56 mmol); ● = HMF yield; ▲ HMF selectivity.

A more extensive screening was further made in [EMIm]Cl with a variation of boric acid concentration from 0 to 4.0 equivalents. The HMF yield increased markedly from 0.1 equivalents and reached a maximum between 0.8 and 1.0 equivalents, where after it gradually declined (Figure 2). The observed selectivity drop at high boric acid

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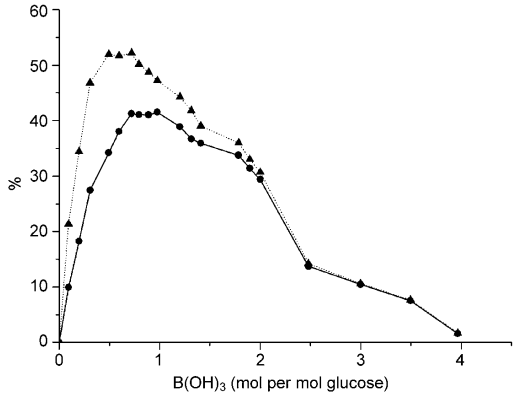

Figure 2. Dehydration of glucose in [EMIm]Cl at 120 °C with different concentrations of boric acid (0–2.24 mmol), ionic liquid (1.0 g), and glucose (100 mg, 0.56 mmol); ● = HMF yield; ▲ HMF selectivity.

content could be a result of formation of more stable sugar–boric acid complexes as well as an increase in humin formation. Increasing the temperature above 120 °C did not result in a higher HMF yield, indicating that the yield of 42 % is the maximum yield obtainable with this procedure.

Dehydration in various solvents: To verify the necessity of the chloride anion in HMF formation, a short survey of the dehydration of glucose was performed in different media such as high-boiling molecular solvents and various ionic liquids together with 0.8 equivalents of boric acid. As shown in Table 1, the best HMF yield was obtained in the chloride containing ionic liquids where [EMIm]Cl still proved to be the best (entries 1–5). Unlike with lanthanide catalysts,[13] no correlation between HMF yield and alkyl chain length on the imidazolium cation of the ionic liquids could be observed. Interestingly, methylimidazolium chloride ([MIm]Cl, entry 1) only exhibited about half the yield of [EMIm]Cl. Since [MIm]Cl is a protic ionic liquid one might have presumed this to inhibit the formation of more stable fructose–borate complexes as is the case with a higher proton concentration in aqueous environments.[21] In the examined non-halide containing ionic liquids, HMF formation was only observed in 1-ethyl-3-methylimidazolium ethylsulfate ([EMIm][$C_2H_5OSO_3$]), choline methylsulfate ([Choline]-[$MeOSO_3$]), 1-ethyl-3-methylimidazolium methylsulfate ([EMIm][CH_3OSO_3]), with a yield of 6 %, suggesting that the sulfate ion was of some importance (entries 6, 7 and 12). The highest yield for the high-boiling molecular solvents was obtained in DMSO (entry 15) with 13 %. All these results substantiate the crucial role of the chloride in the conversion of hexoses to HMF in ionic liquids. The reaction was also performed in ethylene glycol (entry 17) to investigate what effect a competing diol functionality had on the catalytic performance. This resulted in no conversion of glucose to HMF, which was probably caused by stronger binding of the borate to the bulk solvent compared with that of glucose. Dehydration attempts were also made using $NaBF_4$ and sodium tetraborate as boron source in [EMIm]Cl, but resulted in HMF yields below two percent. This suggested that not only was the chloride anion vital, but also the nature of the boron source. The effect of water on the [EMIm]Cl/$B(OH)_3$ system was also tested. Up to five weight percent of water in the reaction mixture induced no detrimental effect on HMF formation, which is consistent with what previously has been reported.[10] Nevertheless, increasing the water concentration further resulted in a significant decrease in HMF yield and above 30 % no HMF was formed. The fact that anhydrous or near anhydrous conditions was essential for progression of the reaction suggests that presence of water forms hydrated chloride ions which are unable to take part in the reaction, in accordance with the mechanism described by Binder and Raines.[16]

Table 1. Dehydration of glucose in various solvents with boric acid as catalyst.[a]

Entry	Solvent	Yield HMF/%	Selectivity HMF/%
1	[MIm]Cl	19	20
2	[EMIm]Cl	41	43
3	[BMIm]Cl	14	30
4	[HMIm]Cl[b]	32	47
5	[OMIm]Cl[c]	26	41
6	[EMIm][CH_3OSO_3]	6	57
7	[EMIm][$C_2H_5OSO_3$]	6	8
8	[EMIm][$AlCl_4$]	0	0
9	[EMIm][OAc]	0	0
10	[EMIm][$N(CN)_2$]	0	0
11	[BMIm][$N(CN)_2$]	0	0
12	[choline][CH_3OSO_3][d]	6	25
13	DMF[e]	7	11
14	NMP[f]	2	23
15	DMSO	13	37
16	α-butyrolactone	0	0
17	ethylene glycol	0	0

[a] Reaction conditions: 1.0 g solvent, 100 mg (0.56 mmol) glucose, 27.5 mg (0.44 mmol) boric acid, 120 °C, 3 h. [b] [HMIm] = 1-hexyl-3-methylimidazolium. [c] [OMIm] = 1-octyl-3-methylimidazolium. [d] [Choline] = *N*,*N*,*N*-trimethylethanolammonium. [e] DMF = dimethylformamide. [f] NMP = *N*-methyl-2-pyrrolidone.

Dehydration of fructose: As mentioned above, fructose can be dehydrated directly to HMF in [EMIm]Cl without a catalyst.[15] To bring further clarity to whether the boric acid is actually catalyzing the direct conversion to HMF, or merely the isomerization of glucose to fructose, experiments with fructose as starting compound were needed.

In Figure 3 the results from experiments with fructose as starting material together with various boric acid concentrations are depicted (selectivity is excluded from the graph since the conversion was between 98 and 100 % in all reactions). At low boric acid concentrations, that is, less than 0.2 equivalents, the obtained HMF yield was high around 80 %. Increasing the boric acid content further brought about a gradual decrease in yield, which was even larger than that for glucose. This clearly indicated that boric acid first and foremost promoted the isomerization of glucose to fructose and that a higher concentration inhibited further reaction

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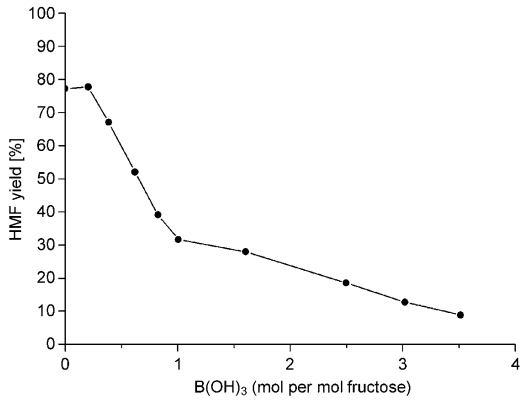

Figure 3. Dehydration of fructose in [EMIm]Cl at 120 °C with different concentrations of boric acid (0–1.96 mmol), ionic liquid (1.0 g), and fructose (100 mg, 0.56 mmol).

due to strong binding of boric acid to fructose. When the boric acid concentration was increased beyond 2.0 equivalents, the HMF yield was even less than 10 %. At boric acid contents higher than what corresponds to two moles of boric acid per mole fructose one would assume the complex with the sugar bound to two borate molecules to predominate. These complexes are likely to be more stable than mono-borate complexes of fructose, something which was also observed in earlier work by Takasaki[24] when enriching fructose from glucose with glucose isomerase.

Dehydration of various carbohydrates: In the light of the good dehydration results obtained with glucose, we wanted to expand our boric acid–ionic liquid reaction system to the dehydration of other carbohydrates. The direct conversion of polysaccharides such as cellulose and starch is highly desirable for a cost competitive process to make HMF. In Figure 4 our results on the various sugars or polymers of glucose capable of forming HMF are summarized.

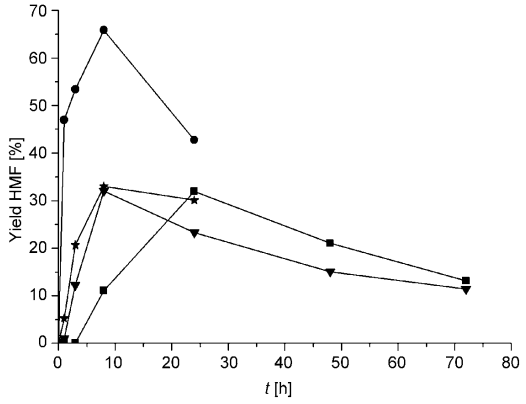

Figure 4. Dehydration of various carbohydrates in [EMIm]Cl at 120 °C with 0.5 equivalents of boric acid (1.0 g ionic liquid and 100 mg carbohydrate: ★ maltose, ● sucrose, ■ starch, ▼ cellulose.

As expected, sucrose, consisting of a linked fructose unit and glucose unit gave the highest HMF yield of 66 %. Maltose, a glucose dimer only amounted to 33 % which was on the same level as cellulose and starch. Reaction times for obtaining the maximum HMF yield varied from 24 h for starch, to 8 h for cellulose and the disaccharides. For comparison, all samples in Figure 4 were dehydrated using 0.5 equivalents of boric acid. Increasing the boric acid amount to one equivalent actually resulted in a decrease in HMF yield for all carbohydrates, most likely due to the fact that glucose is formed in situ from depolymerization and present in a much lower concentration than in the glucose experiments.

Computational study: The results obtained from the experimental work warranted a supplementary study using molecular modeling to elucidate the reaction mechanism in detail. In particular, we were interested in determining how the presence of boric acid affected the relative energies of the various intermediates along the reaction pathway. From the literature the most feasible mechanisms could be narrowed down to two different pathways[28–33] where the rate-determining reaction step consists of either, a) hydride transfer from C2 to C1, or b) the formation of an ene–diol intermediate (also known as Lobryde Bruyn–van Ekenstein isomerization).[34] For the enzymatic isomerization by glucose isomerase deuterium labeling at the C2 position of glucose has pinpointed the route to go via a 1,2-hydride shift.[33] Recently, a detailed study of the chromium(II) chloride catalyzed reaction was published by Pidko et al.[35] In analogy to the enzymatic pathway the authors proposed a dinuclear chromium(II) complex which facilitates the rate-determining hydride shift from C2 to C1. An alternative mechanism involving several protonation and deprotonation steps can also be envisioned, in which a high-energy intermediate ene–diol is formed. The results from the calculations of different complexes and intermediates along the isomerization pathways are illustrated in Figure 5.

Reaction pathway without boric acid: Starting from β-glucopyranose (**1a**) protonation of the anomeric oxygen, followed by ring-opening and depronation gives the corresponding open-chain form of glucose (**1b**) with a relative energy of 20 kJ mol^{-1}. The protonated open-chain glucose is a high-energy intermediate (**1c**, 141 kJ mol^{-1}). An alternative deprotonation route could also be envisioned but when glucose was deprotonated in the 2-position there was a proton shift from O3 during minimization thus resulting in a structure with O3 deprotonated which is no longer en route to the ene–diol (relative energy 28 kJ mol^{-1}, not shown). From the protonated form of glucose formation of the neutral ene–diol intermediate is very favorable (**1d**, 54 kJ mol^{-1}). We have located the transition state for the direct hydride shift TS_{1b-1e} but found the energy to be prohibitively high (183 kJ mol^{-1}). From the ene–diol intermediate additional protonation can lead to formation of protonated fructose (154 kJ mol^{-1}, not shown) although in this case

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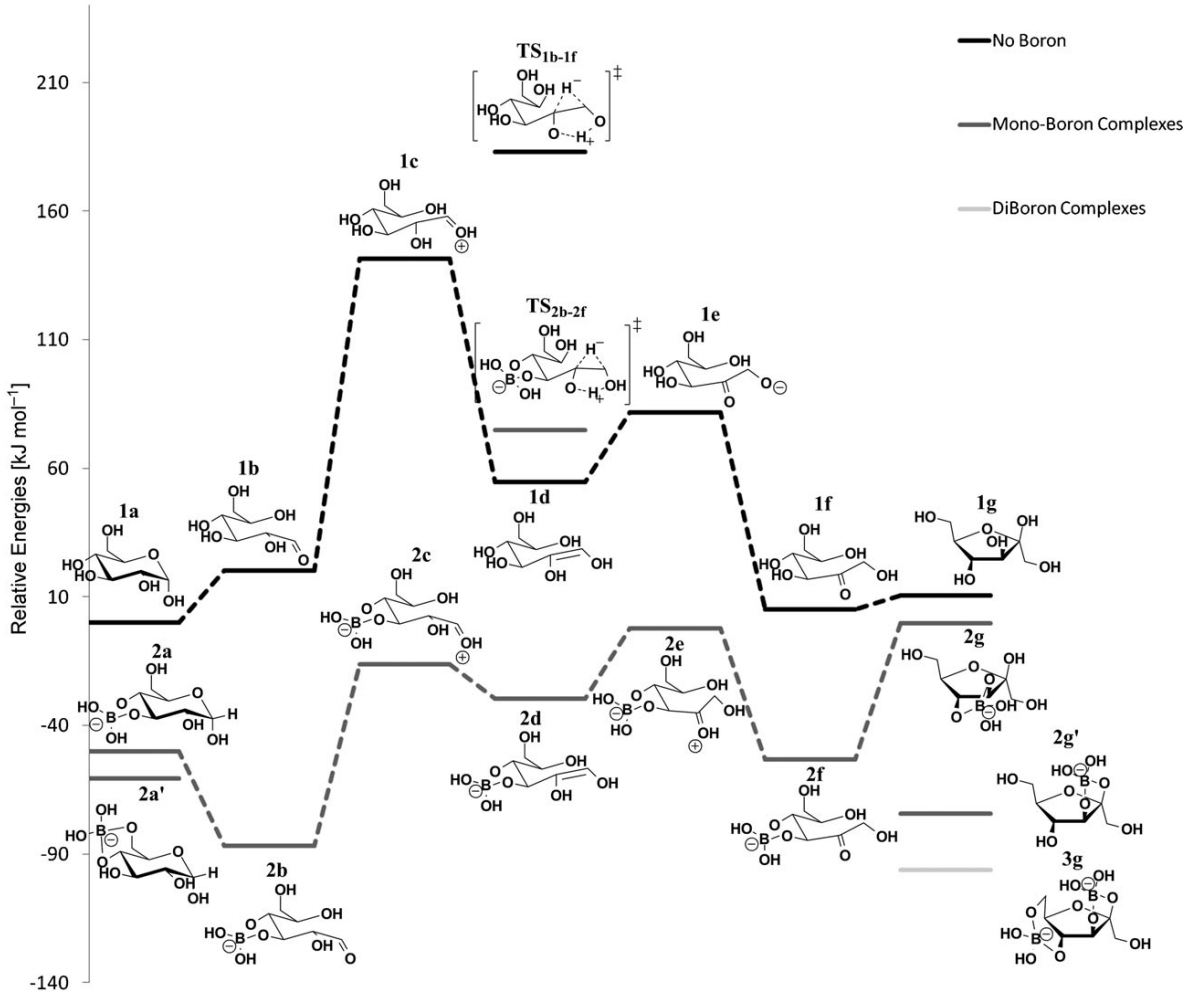

Figure 5. Overview of the two reaction pathways for isomerization of glucose to fructose. The stabilizing effect of boric acid coordination along the reaction pathway is clear.

the deprotonated form of fructose is significantly more favored (**1e**, 82 kJ mol^{-1}). Subsequently, the formation of the open-chain form of fructose (**1f**) can take place, which is significantly more stable than the open-chain glucose (relative energy 5 kJ mol^{-1}). Finally, a ring-closure yields the final β-fructofuranose (**1g**), and it should be noted that the overall isomerization is energetically unfavored by 10.4 kJ mol^{-1}.

Reaction pathway with boric acid: For each intermediate we investigated all possible complexes with boron to determine the energetically most favorable coordination site. For glucose we found the complex with boron coordinated in the 4- and 6-position to be most stable. When comparing to the isolated β-glucopyranose the relative energy of the 4,6-boroglucopyronose (**2a′**) is −60.5 kJ mol^{-1}. Although this comparison involves molecules of different charge the size of the molecules is large enough to allow for reasonable solvation energies. Interestingly, with boric acid present the following ring-opening is now energetically favored resulting in the generation of the open-chain glucose with boron coordinated to the 3- and 4-positions (**2b**). Since the ring-opening probably is faster than boric acid repositioning we have started the pathway for isomerization with the 3,4-boroglucose (**2a**). It is clear that the chelating effect of the boric acid results in a stabilization of the open-chain analogue where the O-B-O angles are close to the optimum for a tetrahedral geometry (107.5 and 109.3°, optimum 109.5°) compared with the closed form where they are either too small 3,4-boroglucose (104.4 and 108.8°) or too large 4,6-boroglucose (113.4 and 115.3°). Protonation of O1 is more favorable than in the absence of boric acid (**2c**, −16 kJ mol^{-1}), which is probably because it is facilitated by the negatively charged boric acid. Subsequent proton transfers results in the formation of the ene–diol intermediate which also has boron coordinated in the 3- and 4-position (**2d**, −29 kJ mol^{-1}). Also in the presence of boric acid we succeeded in locating the transition state for the hydride shift (TS_{2b-2f}, 75 kJ mol^{-1}) but also here the energy is significantly higher than for the

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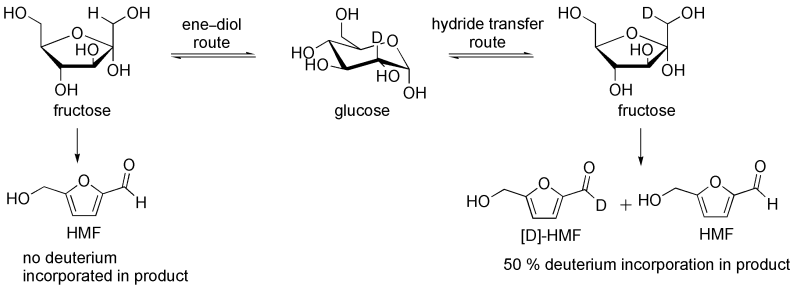
route involving successive proton transfers. From the ene–diol intermediate additional proton transfers can result in the formation of the protonated, open form of 3,4-borofructose (**2e**) with a relative energy of $-2\,kJ\,mol^{-1}$. Deprotonation can give a quite stable open form of 3,4-borofructose (**2f**, $-53\,kJ\,mol^{-1}$), from which a final ring-closure furnishes the fructofuranose with boron coordinated in the 3- and 4-position (**2g**) with a relative energy of $0\,kJ\,mol^{-1}$. Alternatively, a rearrangement of the boric acid moiety to the 2,3-position is very favorable (**2g′**, $-74\,kJ\,mol^{-1}$), something which has also been confirmed by NMR studies where **2g′** appeared to be the most prevalent monoborate complex of fructofuranose.[21] Further on, one could imagine the structure being further stabilized as a very unreactive 2,3,4,6-diborofructose complex (**3g**, $-96\,kJ\,mol^{-1}$). We believe this significant stabilization of the diboron complexes of fructose (both open and closed forms) is responsible for the observed decrease in efficiency when the boric acid/glucose ratio surpasses 1.5 (see Figure 2) and the strong inhibition when converting fructose to HMF (see Figure 3). For the route with monocoordinated boric acid the overall transformation from β-glucopyranose to β-fructofuranose is energetically favored by $14\,kJ\,mol^{-1}$ which explains the increased rate of isomerization in the presence of boric acid. It can be seen that the effect of boron is both to lower the energy of the ene–diol intermediate relative to the glucose and also to increase the exothermicity of the overall isomerization from glucose to fructose.



Scheme 3. Theoretical amount of deuterium incorporated in HMF by the two possible isomerization mechanisms.

Dehydration of 2-[D]-glucose: In order to finalize an overall mechanism for the entire dehydration of glucose to HMF one of the isomerization mechanisms mentioned above would have to be ruled out. By reacting glucose deuterated at the C2 position a substantially different ratio of isotope-labeled products would be obtained. An ene–diol mechanism would expel all the deuterium into the solvent and form the ketone on the C2 position of fructose. The HMF product would therefore in theory have no deuterium incorporation though some minor exchange with the solvent might be expected. In contrast, the 1,2-hydride shift mechanism would result in a fructose-species containing 100% deuteration at the C1 position. Accordingly, further reaction to HMF would theoretically result in a product mixture in which 50% deuterium would be retained on the aldehyde based on the established mechanism of HMF formation from fructose.[16,36,37] The possible reaction scenarios are illustrated in Scheme 3.

We reacted 2-[D]-glucose using the standard dehydration procedure and studied the resulting HMF by NMR and GC/MS methods. This experiment showed that less than five percent deuterium was incorporated in the final HMF product (see Supporting Information). This result was compatible with an ene–diol mechanism and the small amount of deuterium actually incorporated could be explained by H/D exchange with the bulk. Since the reaction was performed under anhydrous conditions, a limited number of protons are available and consequently some of the deuterium atoms expelled in the first step could be available for incorporation further on during the course of reaction. Interestingly, the experiment showed that the isomerization of glucose to fructose using the borate–ionic liquid system proceeded via a different mechanism than that reported for the enzyme glucose isomerase[33] which reacts via a 1,2-hydride-shift mechanism.

Based on this experiment, the results from the DFT calculations and previous work,[16,36,37] we could propose a putative mechanism for the complete reaction of glucose to HMF promoted by boric acid in imidazolium chlorides. As shown in Scheme 4, the glucose–borate complex **2a** gives a favorable transition to **2g** via the ene–diol intermediate **2d**. When **2g** loses its borate and forms free fructose it can proceed by two different pathways: either react further to HMF (pathway a) or form the more stable 2,3-borate complex **2g′** (pathway b). The energy of **2g** is higher than that of **2g′** because the boric acid is bound *trans* to the diol functionality of fructose, whereas it in the latter case is bound *cis*. Evidently, the first step of fructose dehydration to HMF is made impossible in complex **2g′** since the oxygen on C2 is bound to boron and consequently water cannot be eliminated. Once **2g′** is formed it can in principle react further with another borate to form the diborate complex **3g**, which is even more stable than **2g′**. This would explain the lower HMF yield at a boric acid content above 1.0 equivalent mentioned in the previous section. When the reaction is complete the boric acid is bound up as these stable borate esters.

The mechanism of HMF formation from fructose has been debated over the years, where both a pathway with cyclic intermediates[36–40] as well as an open-chain mechanism[41–45] have been proposed. Through extensive experimental work Antal et al.[36] concluded that the cyclic mechanism is the most plausible of the two and the cyclic intermediate **8** was recently identified through an NMR study.[37]

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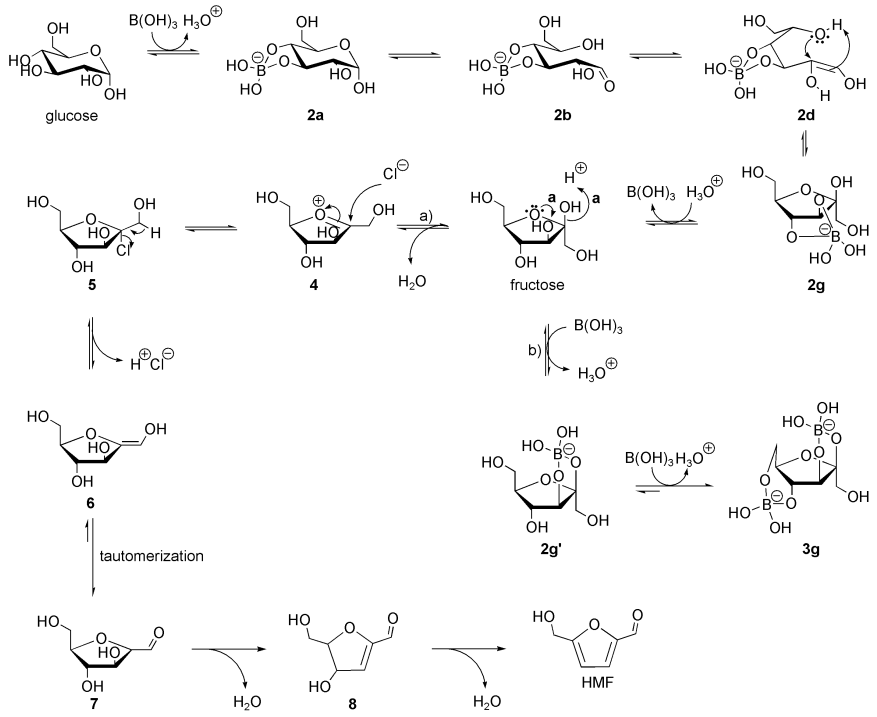

Scheme 4. Putative mechanism for the dehydration of glucose to HMF in imidazolium chlorides with boric acid as promoter.

In the mechanism we have depicted the chloride ion acting as a nucleophile, but it could in principal also be acting as a base as proposed by Binder and Raines.[16]

Conclusion

The boric acid–ionic liquid reaction system presented here is the first metal-free system that catalyzes the conversion of glucose and its polymeric counterparts to HMF. Even though the yields do not surmount what has been achieved so far with chromium catalysts,[15] our results introduce a new class of promoter not based on transition metals, which could prove more practical for scaled up applications where utilization of metals might be questionable from an environmental viewpoint.

The main obstacle with the boric acid–ionic liquid system is the formation of stronger fructose–boric acid complexes such as **2g′** which in due course stops the isomerization by binding up boric acid and at the same time blocking the elimination of water in the first step of the conversion to HMF. The idea of adding a competitor for fructose as a complexation agent falls on the fact that glucose forms weaker complexes than fructose. Such a complexation agent would be an even stronger competitor to glucose and would most likely have the consequence of inhibiting the isomerization of glucose to fructose, something which was evident when performing the reaction in ethylene glycol where no HMF was formed. The challenge for the future development of this system is therefore to find a catalyst for the dehydration of fructose in [EMIm]Cl which does not have a detrimental impact on the boric acid promoted isomerization of glucose to fructose. This could be achieved by screening the reaction together with different catalysts known for catalyzing the dehydration of fructose in ionic liquids. The additional catalyst must naturally meet the criteria of being green and sustainable to obtain a system that would be advantageous to the previous transition metal systems. An alternative to this approach could imply boric acid derivatives which possibly display a different behavior towards isomerization.

Another vital aspect of the introduced reaction system is the ionic liquid. The structure of the cation has evidently a momentous impact on the HMF yield. As mentioned in the previous section, there is no clear reactivity pattern regarding the chain length of the alkyl group on the alkylmethylimidazolium ion. Extended screening of other cations might therefore result in the discovery of a cation that would enhance the HMF yield even more or give a rational explanation for the superior performance of the 1-ethyl-3-methylimidazolium ion.

We believe that with extensive experimental work and modeling on different boric acid based catalytic systems the yields of HMF could be enhanced and be a strong competitor to other catalysts in a future biopetrochemical industry.

Experimental Section

Materials and equipment: All chemicals were used as received. D-glucose (99.5%), 2-[D]-D-glucose (98 atom% D), dimethyl sulfoxide (98%), cellulose (powder, ca 20 micron), dimethylformamide (99%), α-butyrolactone (98%) and *N*-methyl-2-pyrrolidone (99%) were purchased from Aldrich. Boric acid (puriss), starch (p.a.) and D-fructose (puriss) were purchased from Riedel-de Haën. Ethylene glycol (normapur) and D-maltose (p.a.) were purchased from Prolabo. Sucrose (99%) was purchased from Alfa Aesar. [EMIm][$N(CN)_2$] (98%), [choline][CH_3OSO_3] (98%) and [EMIm][$C_2H_5OSO_3$] (98%) were purchased from Solvent Innovation, while all other ionic liquids were obtained from BASF (>95%). The dehydration experiments were performed under nitrogen atmosphere using a Radley Carousel 12 Plus Basic System with temperature control (+/−1 °C). All samples were analyzed by HPLC (Agilent 1200 series, Bio-Rad Aminex HPX-87H, 300 mm × 7.8 mm pre-packed column, 0.005 M H_2SO_4 mobile phase, 60 °C, 0.6 mL min^{-1}). The HMF yields and selectivi-

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ties were based on conversion of glucose and confirmed by calibration of standard solutions of the products and reactants involved.

General dehydration procedure: A 40 mL reaction tube was charged with ionic liquid (1 g) and boric acid (34.6 mg, 0.56 mmol) and heated at 100 °C for 1 h. Glucose (100 mg, 0.56 mmol) or different carbohydrate (0.56 mmol) was then added and the solution stirred for 3 h at 120 °C. After reaction the reaction tube was cooled in an ice bath and water (5 mL) added. The solids were filtered off and the filtrate analyzed by HPLC. Alternatively filtrate was extracted with ethyl acetate (3 × 30 mL) and the solvent then removed in vacuo.

Computational method: Density functional theory (DFT) in combination with the B3LYP functional[46–48] as incorporated in Jaguar version 7.6 from Schrodinger Inc.[49] was used for the calculations. In the current study we employed the LACVP* basis set in Jaguar which uses the Hay–Wadt small-core ECP and basis set for boron[50] and the 6-31G* basis set for the remaining elements. Solvation energies were obtained using the PB-SCRF solvation model[51,52] employing parameters suitable for dichloromethane (dielectric constant 9.08 and probe radius 2.33237 Å). In this model the solvent is described as a continuum, where the molecule is put into a reaction field consisting of surface charges on a solvent accessible surface constructed using a hypothetical spherical solvent probe molecule with the indicated radius.[53] The wavefunction and the reaction field charges are solved iteratively until self-consistency is reached. Physical data on ionic liquids in the literature are still scarce, for example it was not possible to find a dielectric constant for [EMIm]Cl. Thus, we have in the current study used parameters suitable for dichloromethane since its dielectric constant ($\varepsilon = 7.26$) was close to the ones reported of several 1-ethyl-3-methylimidazolium based ionic liquids.[54,55]

In previous projects[56,57] we have found that energies calculated with the continuum solvent model gives a fair correspondence with experimental ratios, but for a quantitative agreement we frequently also need to account for the vibrational component of the free energy. The free energy adjustment was then added to the corresponding energy determined in solvent, to arrive at a composite free energy that is our best estimate of the free energy in solvent.

Acknowledgements

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Synthesis of 5-(Hydroxymethyl)furfural in Ionic Liquids: Paving the Way to Renewable Chemicals

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The synthesis of 5-(hydroxymethyl)furfural (HMF) in ionic liquids is a field that has grown rapidly in recent years. Unique dissolving properties for crude biomass in combination with a high selectivity for HMF formation from hexose sugars make ionic liquids attractive reaction media for the production of chemicals from renewable resources. A wide range of new catalytic systems that are unique for the transformation of glucose and fructose to HMF in ionic liquids has been found. However, literature examples of scale-up and process development are still scarce, and future research needs to complement the new chemistry with studies on larger scales in order to find economically and environmentally feasible processes for HMF production in ionic liquids. This Minireview surveys important progress made in catalyst development for the synthesis of HMF in ionic liquids, and proposes future research directions in process technology.

Introduction

As fossil resources for chemicals and fuels are becoming depleted, the search for new pathways from renewable feedstocks has intensified. One compound that has been under particular scrutiny as a future platform chemical is 5-(hydroxymethyl)furfural (HMF), a six-carbon furan ring obtained from the triple dehydration of hexose sugars.[1,2] HMF has been covered extensively in several reviews,[3–5] and is primarily considered a starting material for other chemicals with important applications, such as monomers for plastics,[6] solvents, or fuels (Scheme 1).[7]

During the past ten years, chemical applications with ionic liquids (ILs) have received increased attention, resulting in an exponential increase in the number of papers published. ILs are normally defined as salts that are liquid below 100 °C and exhibit unique characteristics, such as a negligible vapor pressure, nonflammability, high thermostability, and close to infinite structural variation.[8] Moreover, ILs have remarkable solubilizing ability, which enables large natural polymers such as cellulose to be dissolved at high concentrations.[9-13] Chloride-based ILs have an exceptionally high capacity for dissolving carbohydrates since the extensive hydrogen bonding network that constitutes the structure of the solid carbohydrate is disrupted.[8] One IL in particular that has been widely recognized for its ability to dissolve cellulose is 1-butyl-3-methylimidazolium chloride ([BMIm]Cl), which can dissolve as much as 25% crystalline cellulose by weight.[9] This liquid also possesses the ability to completely dissolve significant amounts of crude biomass, such as banana pulp,[12] poplar, eucalyptus, pine, and oak.[13] Furthermore, the addition of mineral acids to [BMIm]Cl enables the efficient hydrolysis of cellulose to its monomeric constituent glucose.[14,15] Apart from chloride, ILs that incorporate the dicyanamide anion also exhibit very high capacities for carbohydrate dissolution.[10]

The combination of ILs and HMF production has become an important field in its own right, since ILs benefit the selectivity of the conversion of hexoses to HMF and opens up the possibility of one-pot reactions directly from crude biomass. Under aqueous conditions, the selectivity of the reaction is hampered by the irreversible hydrolysis of HMF to formic acid and levulinic acid.[16,17] High yields can be obtained in high-boiling solvents such as DMSO, but suffer from difficult product recovery.[18–20] Another important side reaction in the dehydration of hexoses is the formation of polymers known as humins. These species are formed from different intermediates in the reaction and their rate of formation increases as the concentration of the reacting sugar increases.[21,17] Humin formation remains a problem for HMF synthesis in ILs, but can be significantly reduced as the selectivity towards HMF is very high in many reaction systems.

This Minireview surveys what has been investigated to date in producing HMF from various carbohydrates in IL media, alongside a section on the implications and challenges that are associated with process development of these reactions. A certain focus is set on the future possibilities for environmentally and economically feasible processes using IL reaction media.

Dehydration of Carbohydrates

Carbohydrates constitute 75% of the world's renewable biomass and cellulose, a glucose polymer, is the most abundant.[22] The dehydration of fructose and glucose serve as

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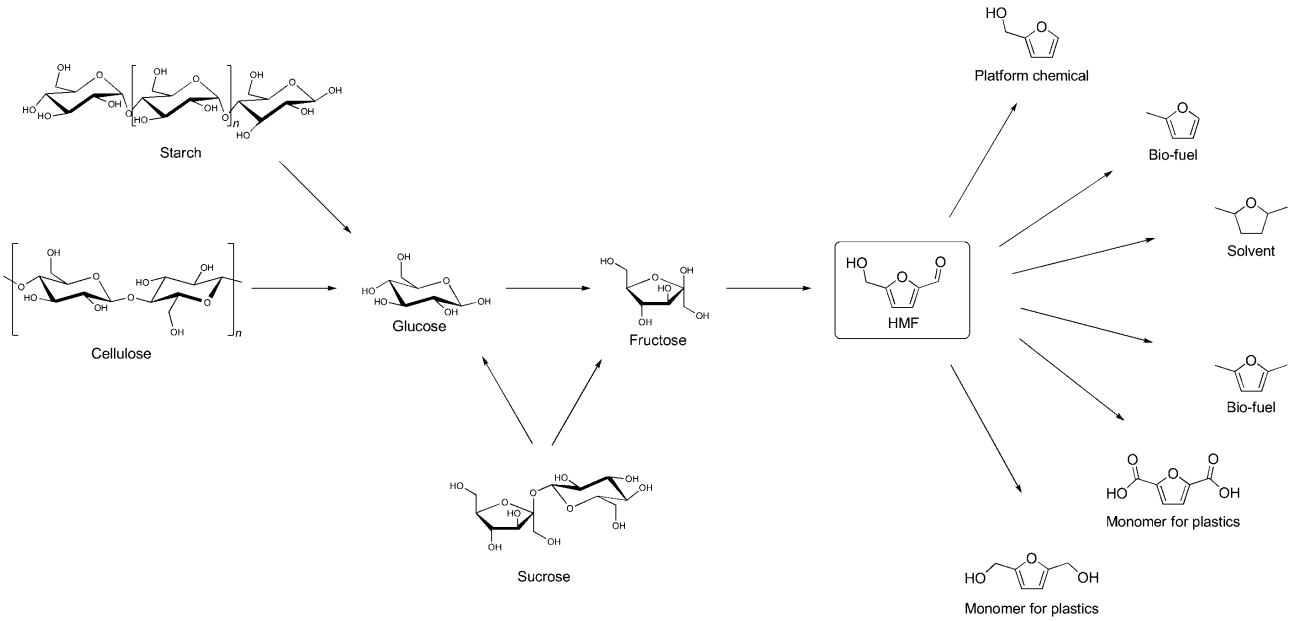

Scheme 1. The synthesis of HMF from carbohydrates and its further derivatization to important chemicals.

model reactions for biomass-derived carbohydrates since the conversion to HMF always involves these sugars in the final reaction sequence. The most noteworthy results in carbohydrate conversion to HMF in ILs are summarized in Table 1.

Table 1. A selection of systems for dehydration of various carbohydrates to HMF in different ionic liquids with or without catalyst.

Entry	Carbohydrate	Solvent	Catalyst	Catalyst amount [mol%]	T [°C]	t [h]	HMF yield [mol%]	Ref.
1	fructose	[MIm]Cl	–	–	90	0.75	92	[40]
2	fructose	[choline]Cl/citric acid	–	–	80	1	91	[50]
3	fructose	[BMIm]Cl	$CrCl_3$	9	100	6	96	[53]
4	fructose	[BMIm]Cl	WCl_6	10	50	4	63	[54]
5	fructose	[BMIm]Cl	HCl	8	23	24	72	[47]
6	glucose	[EMIm]Cl	$CrCl_2$	6	80	3	70	[52]
7	glucose	[BMIm]Cl	$CrCl_3$	9	100	6	81	[53]
8	glucose	[BMIm]Cl	$CrCl_3$	2	n.a.[a]	0.0167	91	[56]
9	glucose	[EMIm][BF_4]	$SnCl_4$	10	100	3	61	[63]
10	glucose	[EMIm]Cl/CH_3CN (5:2)	12-MPA[b]	1	120	3	97	[64]
11	sucrose	[choline]Cl	$CrCl_2$	10	100	0.5	62	[51]
12	sucrose	[EMIm][BF_4]	$SnCl_4$	10	100	3	65	[63]
13	sucrose	[BMIm]Cl/MIBK	$CrCl_3$	14	100	4	100	[42]
14	starch	[EMIm][BF_4]	$SnCl_4$	10	100	3	47	[63]
15	starch	[OMIm]Cl	$CrCl_2$	20[c]	120	1	73[c]	[75]
16	cellulose	DMA/LiCl/[EMIm]Cl	$CrCr_3$; HCl	25; 10	140	2	54	[55]
17	cellulose	[BMIm]Cl	$CrCl_3$	6	n.a.[a]	0.05	62	[72]
18	corn stover	DMA/LiCl/[EMIm]Cl	$CrCl_3$; HCl	10; 10	140	2	48	[55]
19	pine wood	[BMIm]Cl	$CrCl_3$	6	n.a.[a]	0.05	52	[72]
20	inulin	[BMIm][HSO_4]/[BMIm]Cl	Amberlyst 15	75[d]	80	1	82	[78]

[a] Microwave irradiation (400 W); [b] 12-molybdophosphoric acid; [c] wt%; [d] calculated from number of acid equivalents per kilogram catalyst.

Fructose

Dehydration of fructose to HMF has been extensively investigated in aqueous solutions[7,23–34] and organic solvents[18–20,35–37] throughout the 20th century. The first reported example of fructose conversion to HMF in ILs is a somewhat overlooked publication from the early 1980s.[38] Fructose was converted to HMF in pyridinium- and ammonium-based ILs with halides, trifluoroacetate, and tosylate as anions. The best results were obtained with tetraethylammonium bromide, which afforded HMF in 75% yield. This work did not have any immediate impact on the further development of HMF production in salt solutions and it was not until the beginning of the next millennium that carbohydrate conversion in ILs became a hot topic when Lansalot-Matras and Moreau[39] showed that dehydration of fructose in 1-butyl-3-imidazolium-based ILs with [BF_4]$^-$ or [PF_6]$^-$ as anions could be achieved with excellent yields up to 87% using Amberlyst 15 as a heterogeneous acid catalyst and DMSO as cosolvent. They followed up this work by performing dehydration in methylimidazolium chloride ([MIm]Cl), which provided a yield

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of 92% in the neat IL without any additives.[40] Their work prompted intensified activity on the topic and in the years that followed several examples on the dehydration of fructose and other carbohydrates in IL media were demonstrated. The difference in reactivity using a Brønsted acidic or a Lewis acidic IL as catalyst in DMSO was investigated by Bao et al.[41] They found that the Lewis acidic liquid showed a higher efficiency, as well as a higher stability for HMF when left for a longer time in the DMSO/IL mixture. However, when the temperature was increased from 80 to 160 °C, the Brønsted acidic IL afforded a slightly higher yield. The employment of Brønsted acidic ILs for the dehydration of fructose has been exploited further in recent studies, both as neat ILs[42,43] and as additives.[44,45] In addition, there have been examples in which addition of a Brønsted acidic to a non-acidic IL markedly promoted the reaction rate of fructose dehydration.[46–48] The use of polyimidazolium salts (PIMS) that were acidified with HCl as catalysts gave yields of 79–84% of HMF from fructose in [BMIm]Cl at 80–100 °C and could be reused 11 times without any detected deactivation.[49]

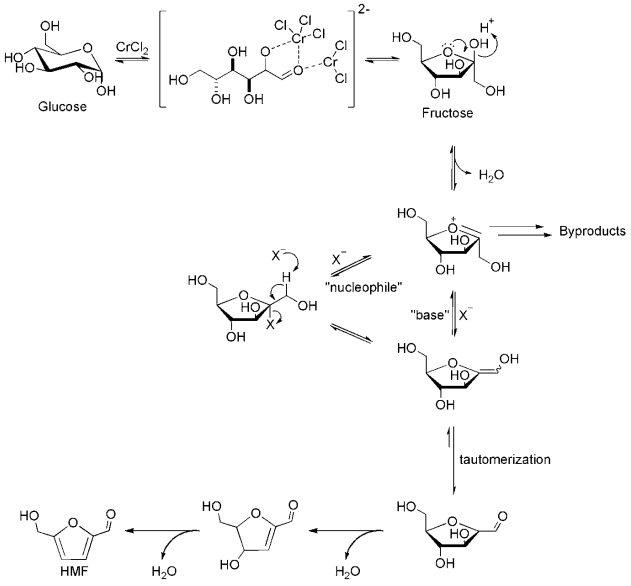
Even though the dehydration of fructose to HMF has been dominated by imidazolium-based ILs, there are some noteworthy exceptions. Making a eutectic mixture of choline chloride and citric acid resulted in a promising catalytic system, which, together with continuous extraction with ethyl acetate, afforded an HMF yield of 91%.[50] The main advantage of this procedure was not only the excellent yield but also the fact that all chemical components involved could be made from renewable sources, even though their main origin today is petrochemical. Choline chloride was further explored by Ilgen et al.[51] to make highly concentrated mixtures of fructose (up to 50 wt%), which resulted in solutions that were liquid below 100 °C, far below the normal melting point of pure choline chloride, which is 300 °C. These mixtures could furnish HMF yields from fructose up to 67% by the addition of *p*-TsOH as catalyst. By increasing the concentration even further, Li et al.[48] managed to dissolve 67 wt% fructose in [BMIm]Cl and with the addition of HCl as catalyst obtained a yield of HMF of 51%.

Chromium chloride is a catalyst that primarily promotes the dehydration of glucose to HMF.[52] Nevertheless, the use of chromium(II) or chromium(III) chloride together with N-heterocyclic carbene (NHC) ligands resulted in HMF yields of up to 96% in [BMIm]Cl.[53]

The examples above have all required temperatures of 80 °C or more to attain full, or nearly full, conversion. However, recent work has shown that the dehydration of fructose to HMF can be achieved with close to full conversion at ambient temperature using [BMIm]Cl as solvent together with WCl_6 as catalyst.[54] The yield was enhanced further when using continuous extraction with THF. In a very recent publication, Lai and Zhang[47] argued that the catalytic effect was present even in the absence of metals. Adding concentrated aqueous HCl to a mixture of [BMIm]Cl and fructose afforded a low-viscosity liquid at ambient temperature which, after 24 h, resulted in an HMF yield of 72%.

Glucose

The conditions by which fructose is converted into HMF are normally ineffective on glucose.[39] A major breakthrough came in 2007 when Zhao et al.[52] published their pioneering work showing that chromium(II) chloride had a remarkable effect on the dehydration of glucose in 1-ethyl-3-methylimidazolium chloride ([EMIm]Cl) leading to an HMF yield of 70%. A number of other transition metal chlorides were also used as catalysts, but they only provided HMF yields below 10%. A higher catalytic effect was ascribed to $CrCl_2$ than to $CrCl_3$, something which has been questioned in later studies. Nevertheless, their work prompted an intense search to further exploit the chromium system as well as finding other catalysts for the direct conversion of glucose to HMF. Binder and Raines[55] made an extensive study on glucose dehydration in dimethylacetamide (DMA) with the addition of halide salts. Adding 10 wt% LiCl or LiBr along with $CrCl_2$, $CrCl_3$, or $CrBr_3$ resulted in HMF yields up to 80%. A putative mechanism was further put forward in which the vital role of the halide ion was made evident (Scheme 2). They did not find a significant activity difference



Scheme 2. Proposed mechanism for glucose dehydration catalyzed by chromium chloride.[29,52,55,57]

between Cr^{II}- and Cr^{III}-based catalysts, which indicated that the oxidation state of the chromium was not decisive. Yong et al.[53] attained an HMF yield of 81% by the use of a NHC–chromium system in [BMIm]Cl, which also exhibited no significant difference between the two oxidation states of chromium. The highest reported yield for HMF from glucose with $CrCl_3$ was made in [BMIm]Cl under microwave heating.[56] The catalyst loading was low (2 mol%) in comparison to other studies and the maximum yield was reached after 1 min.

The chromium-based catalysts have to date only exhibited superb performances in imidazolium-based ILs. Attempts in

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other mixtures have yet to give comparable results; for example, a eutectic mixture of glucose and choline chloride resulted in an HMF yield of 45% with Cr^{II} and 31% with Cr^{III}.[51] This is also the only work besides the original work in the group of Zhang[52] that displayed a difference in catalytic performance between the two chromium species. The mechanism of the chromium-catalyzed conversion of glucose to HMF was thoroughly investigated using density functional theory (DFT) calculations by Pidko et al.[57] The study concluded that the dimer complex of $CrCl_2$ lowered the energy for the transition state of the isomerization of glucose to fructose. The transition state was taken to be the hydride shift as in the enzyme catalyzed isomerization with glucose isomerase[58] and the $CrCl_2$ catalyzed conversion of xylose to furfural.[59] A detailed mechanism of glucose dehydration via fructose is shown in Scheme 2. Another mechanism for the isomerization of glucose to fructose can also be envisioned. It is well known that glucose can be isomerized to fructose under basic conditions in aqueous solutions, something that has been employed in supercritical water and organic solvents where both a solid acid catalyst and a basic catalyst have been used simultaneously.[30,31,60,61]

Lanthanide(III) salts have also been investigated as catalysts for the conversion of glucose to HMF.[62] The use of the strongest Lewis acid $Yt(OTf)_3$ resulted in the highest HMF yield of 24% and the catalytic effect increased with increasing atom number in the lanthanide series. An increase in yield was also observed when the chain length of the alkyl groups on the imidazolium cation increased, that is, 1-octyl-3-imidazolium chloride ([OMIm]Cl) had a significantly higher yield than [EMIm]Cl. This phenomenon has not been observed with other catalyst systems where [EMIm]Cl has been superior or equivalent to other methylimidazolium chlorides.[52]

Even though the best yields for the conversion of glucose to HMF have been obtained with chloride- or other halide-containing ILs, a study in 1-ethyl-3-methylimidazolium tetrafluoroborate ([EMIm][BF_4]) showed that $SnCl_4$ could function as a catalyst for glucose dehydration, with an HMF yield of 61%.[63] Interestingly, both the yield and the selectivity for HMF were higher in [EMIm][BF_4] than both [BMIm]Cl and DMSO when $SnCl_4$ was employed as a catalyst.

The best catalytic system for glucose dehydration hitherto was demonstrated in a very recent publication using 12-molybdophosphoric acid (12-MPA) in [EMIm]Cl with acetonitrile as cosolvent, which offered virtually quantitative yield of HMF.[64] The yield was significantly enhanced by addition of acetonitrile and [BMIm]Cl was equivalent to [EMIm]Cl in performance, whereas 1-butyl-3-methylpyridinium chloride ([BMPy]Cl) and 1-butyl-2,3-dimethylimidazolium chloride ([BDMIm]Cl) induced a lower catalytic effect.

To date, only one example of nonmetal-catalyzed dehydration of glucose to HMF has been reported. In this work, boric acid was utilized as a promoter in [EMIm]Cl, which resulted in an HMF yield of 43%.[65] A supporting NMR spectroscopic study with glucose-2-d_1 confirmed that the conversion of glucose to fructose proceeded via an ene-diol mechanism as opposed the chromium catalyzed isomerization.

The synthesis of HMF from hexoses other than fructose and glucose has very few examples in the literature. An interesting exception is the conversion of red seaweed to HMF via the hexose 3,6-anhydrogalactose in several ILs where choline hydrogensulfate ([choline][HSO_4]) proved to be best with regard to sugar yields as well as HMF formation.[66]

Sucrose

Sucrose consists of one fructose and one glucose moiety linked together by a glycosidic bond. This bond is easily hydrolyzed upon heating in ILs whereby the single units of fructose and glucose are exposed to further reaction.[40] Early work by Fayet and Gelas[38] explored the dehydration of sucrose in pyridinium-based ILs resulting in an HMF yield of 30%. Since no other catalyst was present, it is reasonable to believe that the fructose unit was easily converted to HMF whereas the glucose remained unreacted. This was confirmed later when sucrose in [MIm]Cl underwent nearly quantitative conversion to HMF and glucose.[40] Tong et al.[45] made use of a *N*-methylmorpholinium methylsulfonate ([NMM][CH_3SO_3])/DMSO/LiBr system, by which they attained a HMF yield of 48%.

High-concentration solutions of sucrose and choline chloride (50 wt%) together with chromium chloride catalysts resulted in even higher HMF yields.[51] Notably, a significant difference between $CrCl_2$ and $CrCl_3$ was observed, with HMF yields of 62% and 43%, respectively. Chromium chloride was also used as a catalyst in the investigation by Chun et al.[67] using HCl/[OMIm]Cl/EtOAc mixtures, in which the best results were obtained with a sucrose concentration of 50 wt% and an HCl concentration of 0.3 M. Outstanding results were reported by Lima et al.,[42] who claimed quantitative HMF yield when using a [BMIm]Cl/MIBK/$CrCl_3$ system (MIBK: methyl *iso*-butyl ketone), which is surprising since their results for fructose and glucose alone were only 88% and 79%, respectively, under the same reaction conditions.

Good results were further attained in the $SnCl_4$/[EMIm][BF_4] system where 17 wt% solution of sucrose was converted to HMF with a yield of 65%.[63]

Starch and cellulose

The main advantage of using ILs as media for biomass conversion to HMF is, as mentioned above, the possibility to dissolve carbohydrate polymers and subsequently form HMF and its derivatives in one-pot reactions.[9,13] The first prerequisite for successful dehydration of cellulose or starch is that the polymer is easily depolymerized. It has been established that the addition of an acid catalyst to a [BMIm]Cl solution of cellulose enhances the hydrolysis of the glycosidic linkages between the monomers and that the depolymerization is first-order with respect to catalyst concentration.[68,69] The use of Amberlyst 15 DRY (i.e., containing less than 1.5% water) resulted in an ion exchange of the imidazolium cation on the surface of the solid catalyst that released protons into the solution and made the catalyst work homogenously.[69] An extensive study by Sievers et al.[15] explored the hydrolysis and chemical conversion of

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pine wood in [BMIm]Cl. Adding a catalytic amount of trifluoroacetic acid to a solution of pine wood in [BMIm]Cl enabled complete hydrolysis of the carbohydrate fraction to water-soluble sugars at 120 °C, which is relatively mild. Efficient depolymerization has also been achieved with hydrogen gas together with ruthenium and platinum catalysts[70] and $FeCl_2$ in 1-(4-sulfonic acid)butyl-3-methylimidazolium hydrogensulfate.[71]

The second prerequisite for achieving a successful reaction of starch or cellulose to form HMF is that the catalytic system can transform glucose into HMF. Several studies that have dealt with glucose dehydration also involved attempts at direct conversion of cellulose to HMF. Binder and Raines[55] expanded their study on fructose and glucose dehydration in DMA/LiCl/[EMIm]Cl with cellulose and untreated corn stover, which were reacted with chromium(II/III) chloride as catalyst to afford HMF in 54% and 48% molar yield, respectively. The addition of [EMIm]Cl to the DMA/LiCl solution markedly enhanced the yield. The HMF yield from cellulose was increased further to 62% from chemical cellulose and 52% from pine wood by the use of $CrCl_3$ in [BMIm]Cl with microwave irradiation.[72] Extraordinary results were obtained by Zhang et al.[73] when using $CrCl_2$ and [EMIm]Cl, yielding 89% of HMF from crystalline cellulose. Remarkably, they used 20 wt% solution even though the highest reported [EMIm]Cl solution of cellulose is 15.8 wt%.[74] They used NMR spectroscopy as measurement of conversion, a less sensitive analysis method than the normally employed HPLC method.

Few examples on the conversion of starch to HMF in ionic media have been reported. Hu et al.[63] employed the $SnCl_4$/[EMIm][BF_4] system, by which an impressive HMF yield of 47% from starch was obtained. A more extensive study was made by Chun et al.[75] on the conversion of several different starch sources in 1-octyl-3-methylimidazolium chloride ([OMIm]Cl) with $CrCl_2$ as catalyst. The starch was initially dissolved in HCl before the addition of IL and catalyst. In this case, ethyl acetate was also present as an extraction medium. The HMF yields were reported as a weight percentage of the initial dry substance and of which tapioca starch gave the highest yield of 73 wt%.

Inulin

The production of HMF from inulin in ionic liquids has not been as extensively studied as cellulose, since inulin is far less abundant in nature. It is nonetheless interesting as an alternative feedstock since it is a fructose polymer and indigestible by humans and thus does not compete with food production.[76]

The eutectic mixture of choline chloride and organic acids introduced for fructose dehydration[50] was further explored for the direct conversion of inulin to HMF.[77] A yield of 64% was obtained with a mixture of choline chloride and oxalic acid, which unlike the conversion of fructose to HMF was more efficient than the choline chloride/citric acid mixture and showed a significantly higher solubility for inulin. In principal, there is no advantage in using a system efficient for glucose dehydration for inulin conversion which was made evident when Hu et al.[63] employed their $SnCl_4$/[EMIm][BF_4] system on inulin, obtaining a moderate 40% yield, even lower than that obtained for starch using the same conditions. An efficient system was developed by Qi et al.[78] using first [BMIm][HSO_4] as depolymerization liquid followed by the addition of [BMIm]Cl and acidic resin for fructose dehydration. The system yielded 82% of HMF from inulin and is the highest reported to date. An interesting system using [BMIM]Cl/glycerol carbonate in a 10:90 ratio together with a wet Amberlyst 70 acidic resin resulted in a yield of 60%.[79] A major part of the ionic liquid was substituted with glycerol carbonate to reduce the cost and environmental impact of the process.

Process Technology and Scale-Up

To date, the application of ILs for the conversion of carbohydrates into HMF has been limited to the laboratory, using small-scale apparatus. While the availability of some ILs is still limited, the incentive for scale-up will be obvious if conversions such as those to synthesize HMF can be made to operate in an economic fashion. Hence, we postulate here possible processes for scale-up in an attempt to highlight some of the future research required in the field. Potential economic and scalable processes can be divided into two types, dependent upon whether the reaction is carried out in biphasic or single-phase media. Both types of processes will require effective product recovery and IL recovery and recycling in order to keep the cost contribution from the IL to a minimum. Organic solvent used for extraction will also need to be recycled to minimize its cost contribution.

Biphasic process

The biphasic process is characterized by the dissolution of the feedstock in the IL such that the reaction can be carried out in a second reactor vessel with the addition of an immiscible organic solvent and the catalyst (homogeneous or heterogeneous). Agitation in the vessel is of key importance to enable adequate mass transfer by creation of a dispersion of one phase in the other. This is particularly critical given the viscosity and density of the IL relative to the immiscible organic solvent phase. Unlike conventional biphasic reactions with an aqueous phase and a water-immiscible organic solvent the values in the IL biphasic reactor show a considerable difference in viscosity and density. Thus, it is likely that power inputs greater than 5 $W L^{-1}$ will therefore be required, which will also limit the individual vessel size. Nevertheless, if the mixing is too vigorous then a stable emulsion may be formed, which will be difficult to separate in the subsequent settler unit. Following the settler the solvent phase is distilled to separate HMF and the solvent recycled. The IL is stripped of water and recycled. A potential flowsheet is shown in Figure 1.

Hu et al.[50] reported using a biphasic reactor for dehydration of fructose in [choline]Cl/citric acid with ethyl acetate as an extraction solvent. A reaction yield of HMF of 86% was attained, whereas using a single-phase system only gave 78%. The yield could be further improved to 92% by using continuous extraction. Another example of a biphasic process is that by Benoit

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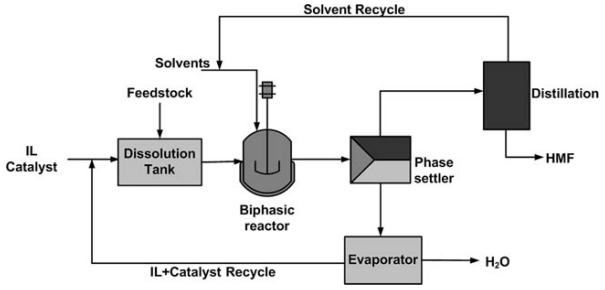

Figure 1. Potential process flow-sheet for biphasic reactor system.

et al.,[79] who significantly reduced the viscosity by making a single-phase mixture of [BMIm]Cl and glycerol (65:35), which in turn formed a two-phase system with MIBK from which HMF could be extracted.

Single-phase process

The single-phase process is characterized by the dissolution of the feedstock in the IL (either neat[38,40,47,51–54,56,62,63,65] or in the presence of a cosolvent such as DMSO[39,41,55,64]) such that the reaction can be carried out in a second reactor vessel with the addition of the catalyst. If the catalyst is heterogeneous, the stirred reactor with a filter can be used since a packed bed is likely to lead to a high pressure drop, given the viscosity of the IL (even with a cosolvent). However, only few studies have mentioned heterogeneous catalysts such as ion-exchange resins[80] or Amberlyst[39] and there appear few advantages. Attention should be given to the use of solid acid catalysts, such as Amberlyst, which may exhibit proton exchange with ionic liquid cation resulting in a much more corrosive reaction mixture than expected.[69,79,81] Regardless of the form of the catalyst, the product would be extracted from the IL by an immiscible organic solvent, such as ethyl acetate,[50] toluene,[39] or diethyl ether,[40] in a subsequent step. Thereafter, the IL would be stripped of water and recycled. Investigations on the effect of humins present in the reaction mixture after IL recycling is needed alongside, if necessary, a good procedure for the separation of humins and IL. The extraction-settler unit needs to be carefully designed as discussed in the section describing the biphasic process. A potential flow-sheet is shown in Figure 2.

If a high HMF selectivity can be maintained at full feedstock conversion, another alternative for product recovery is to use

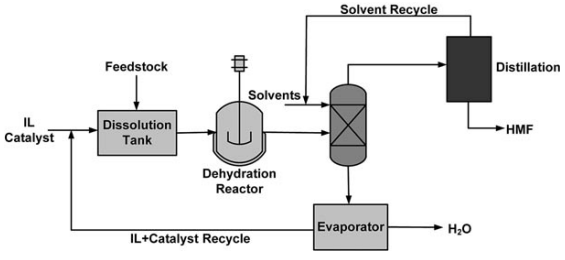

Figure 2. Potential process flow-sheet for single phase reaction system.

distillation of HMF from the IL. The reaction mixture needs to be first sent to an evaporator to remove water formed in the reaction prior to distillation. A potential process flow-sheet based on this option is shown in Figure 3. Although distillation of HMF from IL has not been reported, this option should be possible due to the low vapor pressure of ILs.

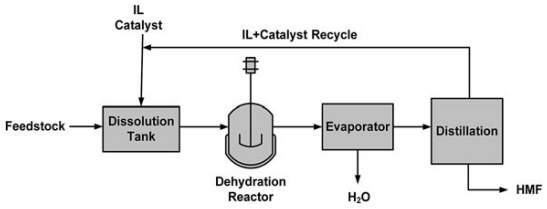

Figure 3. Alternative process flow-sheet for single phase reaction system.

Li et al.[56] suggested a continuous reaction–distillation process for their [BMIm]Cl/$CrCl_3$ system with microwave heating, but have yet to present this idea in practice. The prerequisite for this type of process is that it requires full conversion of feedstocks and can only be applied to reaction media with neat ILs. Qi et al.[82] studied the effect of recycling a [BMIm]Cl/$CrCl_3$ system for the dehydration of glucose, for which five cycles could be performed without loss of activity. After extracting the wet [BMIm]Cl with ethyl acetate, the IL was dried for 24 h.

IL mixtures with DMSO cannot be applied, since removal of DMSO from HMF is very difficult and requires special treatment.[19,83]

Process scale-up

The suggested biphasic and single-phase IL-based processes use conventional process plant and have the advantage of much smaller solvent inventories than non-IL-based processes. Additionally, they provide the important potential for one-pot operation from the feedstock. Clearly, the feedstock choice will also affect the HMF yield and separation requirements downstream and a relatively simple process can be envisioned. However, critical to economic operation is that both processes are dependent upon solvent and IL recycling. From the perspective of design, the biphasic reactor (or liquid–liquid extractor) needs careful consideration. Given the potential market size for HMF, it is clear that continuous operation will be required. Mixer–settler units lend themselves to such an operational mode but, by definition, will operate at less than full conversion to ensure the reaction is completed in an adequate time. Potentially, some of the ILs may be corrosive so suitable materials will be required for construction of parts of the plant in contact with the IL.

Depending on the process, the purity of HMF will vary. HMF obtained from a biphasic process will, depending on the selectivity of the reaction and the purity of the ionic liquid, contain impurities that could make it less valuable as a commodity chemical. A purification step might therefore be necessary.

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Low-temperature recrystallization or sublimation are the most obvious choices, considering the melting and boiling points of HMF. The required purity profile of HMF is completely dependent on its application and, since it is primarily considered to be a platform chemical, purification might in some cases not be necessary prior to derivatization.

The use of green eutectic solvents and glycerol as cosolvent are examples of future competing technologies to IL processes. The advantage of an IL-based process over these is the possibility for high-concentration solutions of cellulose in some ILs, making a one-pot process from crude biomass more feasible.

Outlook

The rapidly growing field of HMF production in ILs from carbohydrates holds great promise for the future. The field is nonetheless in its infancy and a number of issues need to be investigated in detail in the continuous search for realistic large-scale processes. Future research should target an economic analysis of the potential processes outlined herein. In addition, some specific subjects concerning the chemistry and process engineering should be addressed as follows:

- A thorough investigation of the influence of both the cation and the anion of the IL on the reaction outcome and an extensive screening of different ILs are needed to ascertain whether the liquids presented herein are superior in performance.

- The mechanism of glucose dehydration needs to be investigated further for optimized performance and the interaction between the ILs and catalysts should be examined.

- Adequate dissolution and reaction kinetics of the feedstock in the IL and further studies with crude biomass as a feedstock for more realistic conditions.

- Even though there are several excellent papers and reviews on physicochemical properties of ILs,[84,85] more specific property data of the relevant ILs in connection with catalysts and substrates are required, for example, stability, as well as density and viscosity.

- Adequate dispersion of the IL and the immiscible organic solvent (power input and mixing studies will be required at a variety of scales), as well as phase separation of the IL and immiscible solvent following intimate contact and removal of water from the IL prior to recycling (the loss on each cycle of IL will require particular attention) need to be investigated. For continuous operation, an understanding of the conversion–kinetic trade-off, which is necessary for continuous stirred tank reactor (CSTR) operation, requires further studies.

It is our belief that a future cost-effective and environmentally acceptable process of HMF production in ionic liquids should be possible if the points listed above are pursued and thoroughly investigated.

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Keywords: 5-hydroxymethylfurfural · biomass · carbohydrates · ionic liquids · renewable chemicals

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COMMUNICATION

Enzymatic Isomerization of Glucose and Xylose in Ionic Liquids

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In this work glucose isomerase has been found for the first time to catalyze the isomerisation of glucose to fructose in the ionic liquid *N,N*-dibutylethanolammonium octanoate (DBAO). Isomerization was achieved at temperatures of 60-80 °C although a substantial amount of mannose was formed at elevated temperatures via the Lobry-de Bruyn-van Ekenstein transformation. Particularly attractive is that complete recovery of the sugars after reaction was achieved by extraction with aqueous HCl.

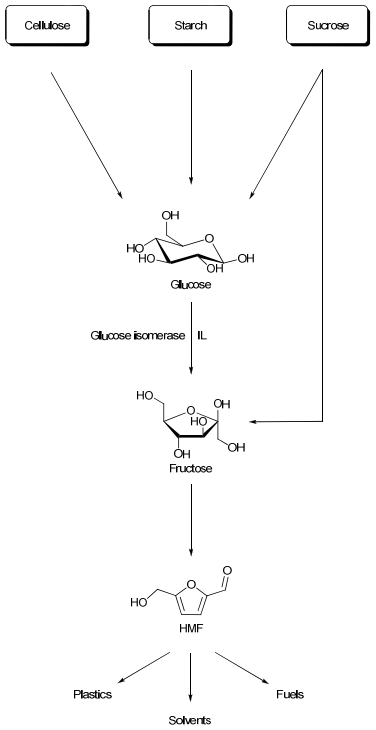
Introduction

The increased demand for sustainable and environmentally benign chemical processes makes enzymes attractive alternatives as catalysts in industrial processes. Enzymes are by virtue most effective in aqueous environment where many chemical substrates and products have low solubility. Therefore the search for alternative solvents in which enzymes have retained activity is of the essence.

Ionic liquids (ILs) are interesting alternatives to conventional organic solvents due to their negligible vapor pressure, non-flammability and unique dissolving abilities for polar compounds and polymers.[1] The study of enzymes in ILs has intensified over recent years and many interesting examples are covered in two excellent reviews by the group of Sheldon.[2,3] In particular lipases have proven to be stable and have retained or improved activity in ILs.[4-11] Other noteworthy examples are the synthesis of aspartame with thermolysin in 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIm][PF_6])[12] and the oxidation of cellobiose with cytochrome c in hydrated choline dihydrogen phosphate ([Choline][dhp]).[13,14]

Glucose isomerase (GI) catalyzes the isomerisation of glucose to fructose and is used for the production of high-fructose corn syrup (HFCS) which is currently one of the most important industrial bioprocesses (Scheme 1).[15] The process is limited by the poor yield of fructose and in spite of significant research on enriching fructose, the process currently requires an expensive chromatographic step to achieve the desired fructose concentration.[15-17] The process usually works in water and examples in the literature on GI in alternative solvents are scarce, nevertheless successful isomerisation has been achieved in aqueous ethanol, indicating that GI can maintain activity at reduced water concentrations.[18] Finding an IL system where GI could exhibit activity would be of significant interest, not only for the food industry, but also since it opens up the possibility of one-pot reactions for future platform chemicals such as 5-hydroxymethyl furfural (HMF). HMF is formed via the triple dehydration of hexoses and is readily obtained from fructose while the conversion from glucose requires special catalysts.[19] HMF and its derivatives are believed to be among the most important platform chemicals of the future biopetrochemical industry.[20] Given the high solubility of carbohydrates in ILs and the sensitivity to hydrolysis of HMF in aqueous solutions, a direct process from glucose to HMF in ILs has the potential to be one of the major industrial processes in a post-petrochemical world.[21]

To the best of our knowledge, no successful enzymatic isomerization of glucose to fructose in ILs has been made. We present here a study of GI in different ILs and show for the first time an IL/GI system that converts glucose to fructose enzymatically.

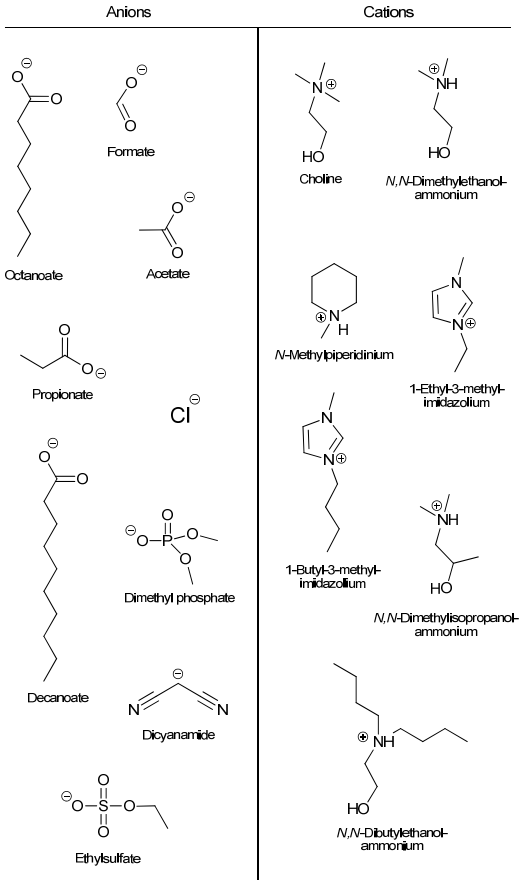


Scheme 1. Isomerization of glucose to fructose and its further derivatization to biopetrochemicals.

Results and Discussion

Screening of GI Activity in Various ILs

GI is in industrial applications primarily used in its immobilized form. Sweetzyme is a GI derived from a strain of the bacterium *Streptomyces murinus* and immobilized by the crosslinking of whole cells with glutarealdehyde.[22] The activity of GI was first screened in several ILs using the immobilized GI Sweetzyme. Examples of anions and cations of the ILs screened are depicted in Scheme 2. Attempts without water, addition of 9 wt% and 18 wt% water were made. Most ILs had a detrimental effect on the enzyme activity whereas others simply did not dissolve glucose in reasonable amounts. In Table 1 the results of the ILs that gave conversion of glucose to fructose after 24 hours are shown. In all cases the isomerization rate was significantly slower than in water. The two ILs most commonly employed for biomass conversion, 1-ethyl-3-methylimidazolium chloride ([EMIm]Cl) and 1-butyl-3-methylimidazolium chloride ([BMIm]Cl) both had a detrimental effect on enzyme activity and afforded no fructose. Most promising results were found using ammonium carboxylates, where *N*,*N*-dibutylethanolammonium octanoate (DBAO) together with 18 wt% H_2O, gave a fructose yield of 52 % after 24 hours. In addition to fructose, 2 % mannose was formed, most likely from fructose via the Lobry-de Bruyn-van Ekenstein transformation.[23] No mannose was formed using any of the other ILs.



Scheme 2. Examples of different ions of the ILs used in the initial screening.

Table 1. Isomerization of glucose to fructose in ILs with Sweetzyme at equilibrium.[a]

IL	Glucose:Fructose ratio (mol:mol)		
	No H_2O	9 wt% H_2O	18 wt% H_2O
N,*N*-Dimethylethanolammonium formate	N/A	95:5	94:6
N,*N*-Dimethylethanolammonium propionate	N/A	77:23	83:17
N,*N*-Dimethylethanolammonium decanoate	N/A	82:18	86:14
Choline propionate	N/A	96:4	95:5
N,*N*-Dimethylbutylammonium propionate	N/A	N/A	87:13
N-Methylpiperidinium acetate	N/A	99:1	91:9
DBAO	N/A	N/A	46:52[b]
N,*N*-Dimethylisopropanolammonium propionate	80:20	82:18	89:11
[Choline][OAc]	94:6	95:5	94:6
[EMIm][OAc]	95:5	95:5	95:5
[BMIm][OAc]	94:6	94:6	93:7
N,*N*-Dimethylethanolammonium formate	N/A	95:5	94:6

[a] Reaction conditions: 100 mg glucose, 0.8-1.0 g IL, 0-0.2 mL H_2O, 30 mg Sweetzyme and 3.3 mg $MgSO_4 \cdot 7H_2O$, 60 °C, 24 h. [b] 2 % mannose present

Glucose Isomerization in DBAO

In Figure 1 the results from the isomerisation of glucose in DBAO over time is shown. After 1 hour around 25 % fructose had formed, which was significantly slower than in water where equilibrium was reached already after 0.5 hours using the same batch of Sweetzyme. After 4 hours in DBAO a glucose-fructose molar ratio of 49:51 was reached after which the fructose amount was stabilized at 52 % whereas the mannose part increased at the expense of glucose over time. The pH of the IL/H_2O-solution was neutral, suggesting that the isomerisation of fructose to mannose was a result of a specific base-catalysis.

Increasing the temperature to 70 and 80 °C retained enzyme activity in DBAO and resulted in reaching the equilibrium, faster and with a greater enrichment of fructose, as expected at elevated temperatures (Figure 2 and 3).[15] At 70 °C a fructose content of 55 % was reached after 4 hours and a correspondingly amount of 58 % at 80 °C. The amount of mannose was also increased and after 24 hours at 80 °C as much as 11 % was reached whereas glucose only amounted to 31 %. No mannose was formed after 4 hours in either case which indicated that a certain amount of fructose was formed before the chemical isomerisation of fructose to mannose was initiated. However, by-product formation was a problem over longer reaction times and after 48 hours significant caramellization of the sugars had taken place. The initial rate constants for all three temperatures in DBAO as well as the corresponding rates in water are listed in Table 2. The reaction was considered to be first order with respect to glucose concentration.

Work-up after complete isomerization was made by extracting the IL with 1 M HCl. A single extraction with an equal volume of

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acid solution to IL resulted in complete recovery of the sugars to the aqueous phase. Water and DBAO formed a homogeneous clear solution when using 18 wt% water and 0.0135 mmol of $MgSO_4$ at temperatures of 60 °C and above, but formed a clear two phase system with 1 M HCl. This provides a separation method that can be suitable for large scale production of these sugar mixtures.

In order to verify that the observed glucose isomerization in DBAO was enzymatic, glucose was left to stir under normal reaction conditions without the addition of Sweetzyme. This resulted in 8 % fructose after 72 hours, confirming that the high fructose yields in the former experiments were a result of catalysis by the active enzyme (Figure 4).

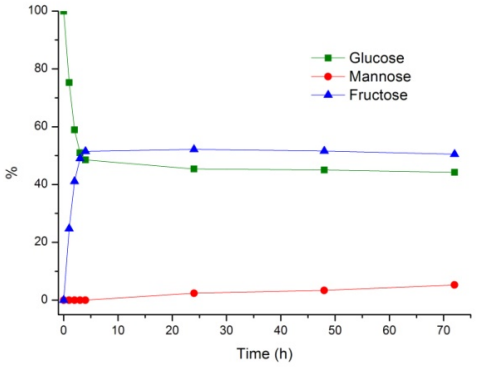

Fig. 1 Enzymatic conversion of glucose to fructose in DBAO at 60 °C. Reaction conditions: 100 mg glucose, 0.8 g DBAO, 0.2 mL H_2O, 30 mg Sweetzyme and 3.3 mg $MgSO_4 \cdot 7H_2O$.

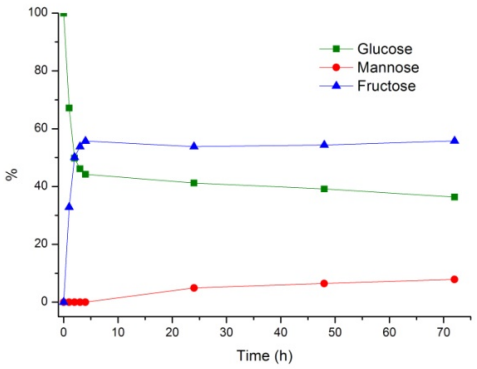

Fig. 2 Enzymatic conversion of glucose to fructose in DBAO at 70 °C. Reaction conditions: 100 mg glucose, 0.8 g DBAO, 0.2 mL H_2O, 30 mg Sweetzyme and 3.3 mg $MgSO_4 \cdot 7H_2O$.

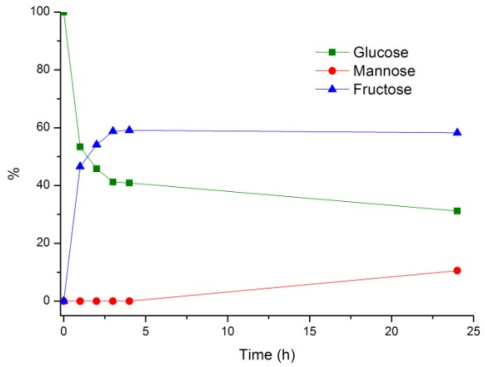

Fig. 3 Enzymatic conversion of glucose to fructose in DBAO at 80 °C. Reaction conditions: 100 mg glucose, 0.8 g DBAO, 0.2 mL H_2O, 30 mg Sweetzyme and 3.3 mg $MgSO_4 \cdot 7H_2O$.

Table 2. Initial rate constants for glucose conversion.

Temperature (°C)	Rate const. DBAO (h^{-1})	Rate const. H_2O (h^{-1})
60	0.27	0.71
70	0.35	1.14
80	0.80	1.46

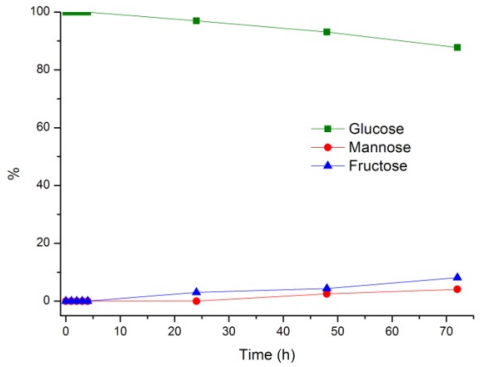

Fig. 4 Conversion of glucose to fructose in DBAO at 60 °C without enzyme. Reaction conditions: 100 mg glucose, 0.8 g DBAO, 0.2 mL H_2O, and 3.3 mg $MgSO_4 \cdot 7H_2O$.

Xylose Isomerization in DBAO

The natural substrate of GI is xylose which is isomerized catalytically in nature to xylulose. The isomerization of xylose to xylulose exhibits a different product distribution upon reaching equilibrium than that of glucose to fructose. The thermodynamic equilibrium between the two pentoses are 86:14 respectively.[24-26] When using our DBAO system equilibrium was reached already after two hours as would be expected since it is the natural substrate of the enzyme (Figure 5).[15] After 24 hours significant degradation had occurred indicated by an increase of several unidentified peaks suggesting that the xylose and xylulose were

less stable in the IL system compared to the hexoses.

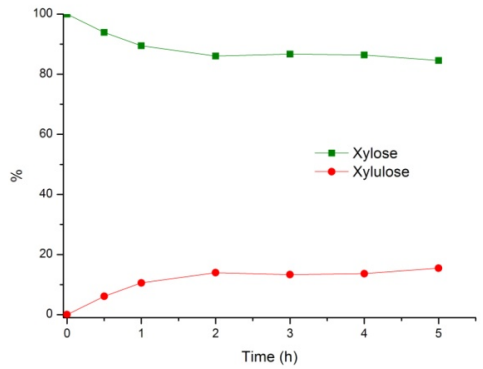

Fig. 5 Enzymatic conversion of xylose to xylulose in DBAO at 60 °C. Reaction conditions: 100 mg xylose, 0.8 g DBAO, 0.2 mL H_2O, 30 mg Sweetzyme and 3.3 mg $MgSO_4 \cdot 7H_2O$.

Experimental

Materials

All chemicals were used as received. D-glucose (99.5 %) and xylose (99 %) were purchased from Aldrich. D-fructose (puriss) was purchased from Riedel-de Haën. [EMIm]Cl and [BMIm]Cl were obtained from BASF while all other ILs were purchased from CLEA Technologies. All experiments were performed using a Radley Carousel 12 Plus Basic System with temperature control (±1 °C). Samples were analyzed by HPLC (Agilent 1200 series, Phenomenex Rezex RCM-Monosaccharide Ca^{2+} (%), 300 x 7.8 mm pre-packed column, MilliQ water as mobile phase, 80 °C, 0.6 mL/min). Peaks were identified from standards of all products and substrates.

General procedure for isomerization

Ionic liquid (0.8-1.0 g), $MgSO_4 \cdot 7H_2O$ (3.3 mg, 0.0135 mmol), water (0-0.2 mL, 0-18 wt%) and sugar (100 mg, 9 wt%) were stirred for 5 minutes and a clear homogeneous solution was obtained. Sweetzyme (30 mg) was added and the reaction was allowed to stir for a maximum of 72 hours. Samples were taken out during the reaction and analyzed by HPLC.

Conclusions

In summary, we have shown the first successful enzymatic conversion of glucose to fructose as well as xylose to xylulose in ILs. During isomerisation of glucose the formed fructose was converted to mannose via the Lobry-de Bruyn-van Ekenstein transformation leading to an accumulation of fructose and mannose at the expense of glucose over time. The activity of the enzyme was lower in ILs in comparison to water resulting in slower reaction rates. Xylose isomerisation was, however, faster in comparison to glucose as would be expected being the natural substrate of the enzyme. It is reasonable to believe that the surface of the enzyme is hydrated and hence facilitates activity even in the presence of the IL. Analogous to the previous report on ethanol,[18] 18 wt% of water was used. In this case, however, solubility of the sugar and $MgSO_4$ - not enzyme activity - was the main reason for using this particular solvent composition.

The conversion of biomass to commodity chemicals is alongside the production of sweeteners the most important future application of this catalytic system. Hence, our work will continue with studies of fructose dehydration to HMF using Lewis and Brønsted acid catalysts like, e.g. WCl_6,[27] $CrCl_3$,[28,29] or HCl[30] in DBAO at elevated temperatures.

We believe that this work provides interesting discoveries concerning the compatibility of GI and ILs and could initiate further studies on GI in alternative solvents. Furthermore, it facilitates opportunities to make a one-pot synthesis of platform chemicals from glucose or its natural polymers.

Acknowledgement

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Notes and references

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Aerobic Oxidation of 5-(Hydroxymethyl)furfural in Ionic Liquids with Solid Ruthenium Hydroxide Catalysts

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Abstract

The aerobic oxidation of 5-(hydroxymethyl)furfural was investigated over solid ruthenium hydroxide catalysts in ionic liquids at elevated temperatures and pressures. Several different catalyst supports were tested in combination with various ionic liquids. The best result was obtained in [EMIm][OAc] at 100 °C with 30 bar of oxygen over $Ru(OH)_x/La_2O_3$ which afforded 48 % of 2,5-furandicarboxylic acid (FDA) and 12 % of 5-hydroxymethyl-2-furancarboxylic acid (HMFCA). Catalytic activity was detected in the ionic liquid after the catalyst was filtered off revealing that the oxidation proceeded partly homogeneously.

Keywords: Oxidation, Supported ruthenium hydroxide, 5-(hydroxymethyl)furfural, 2,5-furandicarboxylic acid, Ionic liquids

1 Introduction

In all segments of the chemical industry oxidations of functional groups play a vital role in the derivatization of chemical compounds. These reactions have traditionally

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been carried out with stoichiometric reagents such as chromium(VI) compounds, permanganate, iodate compounds and peroxy acids which have toxicity issues and produce a large amount of waste compared to the amount of product.[2] In order to relinquish the use of these reagents, the chemical industry, and the scientific community are pursuing oxidations with environmentally benign oxidants such as hydrogen peroxide and molecular oxygen together with efficient and selective catalysts.[3,4]

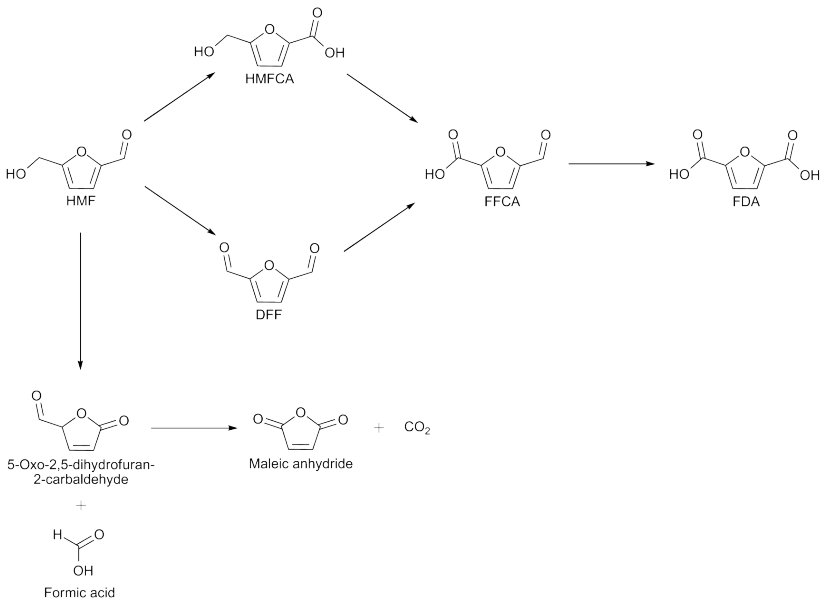
Recently Yamaguchi and co-workers[5] introduced supported ruthenium hydroxides as versatile and highly active catalysts for aerobic oxidations. These catalysts work exceedingly well in connection with common functional group transformations such as oxidations of alcohols[6] and the oxygenation of primary amines to amides.[7]

Ionic liquids (ILs) are interesting alternatives to conventional molecular solvents due to their negligible vapor pressure, redox stability, non-flammability and unique dissolving abilities for polar compounds.[8] The redox stability has allowed oxidations to be widely studied in ILs for several applications such as the oxidative Glaser coupling,[9] oxidations of alcohols to aldehydes or ketones[10] and the oxidation of alkanes.[11] Several examples of epoxidations of alkenes[12] and other miscellaneous functional group transformations[13] in ILs are also found in the literature. In most cases the oxidant is H_2O_2, but also stoichiometric reagents such as NaOCl, Dess-Martin periodate, MnO_2 and *meta*-chloroperoxybenzoic acid (mCPBA) have been reported. The most commonly employed ILs are 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIm]-[BF_4]) and 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIm][PF_6]). The ideal oxidant for green chemical processes is molecular oxygen and aerobic oxidations with homogeneous catalysts in ILs have been reported by numerous groups.[14–16]

Deriving chemicals from biomass has received significant attention among chemists in later years. In particular 5-(hydroxymethyl)furfural (HMF), formed from the dehydration of hexose sugars, has been in the spotlight since it is believed to become an essential platform chemical in the future biopetrochemical industry.[17,18] An important derivative of HMF is 2,5-furandicarboxylic acid (FDA), which is formed by oxidation and is intended to replace terephtalic acid as a monomer in plastics.[19] The catalytic oxidation of HMF was initially studied by the group of van Bekkum using heterogeneous

platinum and palladium catalysts.[20,21] This study has been succeeded in later years with studies on $Co(acac)_3$,[22] gold nanoparticles[23–25] and a more detailed study of platinum catalysts on different supports.[26] The oxidation of HMF proceeds via diformyl furfural (DFF) or 5-hydroxymethyl-2-furancarboxylic acid (HMFCA) to 5-formyl-2-furancarboxylic acid (FFCA) which is rapidly converted to FDA.[20] HMF can also be oxidized to DFF and maleic anhydride selectively using vanadium catalysts.[27–29] The different oxidation products of HMF are depicted in Scheme 1.

The synthesis of HMF from sugars benefits particularly from using certain ILs as



Scheme 1. Different oxidation products of HMF.

solvents, why an overall process from HMF to FDA in ILs would be advantageous.[30] In addition, the exceedingly low solubility of FDA in water and other conventional solvents makes an oxidation process of HMF in ILs by the use of heterogeneous catalysts an interesting option.[31] In such a process the catalyst would be filtered off after complete reaction, followed by the addition of water to the resulting IL/FDA mixture making FDA precipitate. The aqueous IL would then be stripped of water and recycled.

To the best of our knowledge no investigation of heterogeneous catalysts for the

aerobic oxidation of HMF in ILs has been reported. Our objective in this study was to investigate the stability and performance of heterogeneous $Ru(OH)_x$ catalysts on different supports in ILs for the aerobic oxidation of HMF to FDA. The reaction was studied at different reaction conditions and leaching tests of ruthenium were made to investigate the stability of the catalyst in ILs.

2 Experimental

2.1 Materials

5-(Hydroxymethyl)furfural (HMF) (>99%), 2-furoic acid (98%), levulinic acid (LA) (98%), formic acid (FA) (98%), ruthenium(III) chloride (purum), $Mg_6Al_2CO_3(OH)_{16}{\cdot}4H_2O$ (HT), magnetite (>98%), $Ca_5(PO_4)_3(OH)$ (HAp) (>97%), aluminium oxide (>99.9%), zirconium oxide (99%), lanthanum(III) nitrate hexahydrate (99.99%) and sodium hydroxide (>98%) were acquired from Sigma-Aldrich. Ruthenium(III) nitrate hexahydrate (99.9%) and magnesium nitrate hexahydrate (p.a.) were obtained from Merck. Cerium oxide (99.5%) and lanthanum(III) oxide (99.9%) were purchased from Alfa Aesar. Magnesium oxide (p.a.) was purchased from Riedel-de Haën AG. 2,5-Diformylfuran (DFF) (98%) was obtained from ABCR GmbH & Co. 2,5-Furandicarboxylic acid (FDA) (>99%) and 5-hydroxymethyl-2-furan-carboxylic acid (HMFCA) (>99%) were purchased from Toronto Research Chemicals Inc. and dioxygen (99,5%) from Air Liquide Denmark. The ionic liquids 1-ethyl-3-methylimidazolium dicyanamide ([EMIm][$(CN)_2$]) (98 %) and 1,3-dimethylimidazolium dimethyl phosphate ([MMIm][dmp]) (98 %) were purchased from Solvent Innovation, while all other ionic liquids (>95 %) were obtained from BASF. All chemicals were used as received. All $Ru(OH)_x$/support catalysts were synthesized according to literature procedures.[32]

2.2 Apparatus and Analysis

Catalytic oxidation experiments at ambient pressure were performed using a Radley Carousel 12 Plus Basic System, while high pressure oxidation reactions were carried out in stirred Parr autoclaves equipped with internal thermocontrol (T316 steel, Teflon^{TM} beaker insert, 100 ml). All reaction samples were analyzed by HPLC (Agilent 1200 series, Bio-Rad Aminex HPX-87H, 300 mm x 7.8 mm pre-packed column, 0.005 M H_2SO_4 mobile phase, 60 ^{o}C, 0.6 mL/min).

The yields and selectivities were based on conversion of HMF and confirmed by calibration of standard solutions of the products and reactants.

$$\texttt{HMF conversion} = \frac{1 - \texttt{(Amount of HMF)}}{\texttt{Starting amount of HMF}} \tag{1}$$

$$\texttt{Yield FDA/HMFCA/DFF} = \frac{\texttt{Amount of FDA/HMFCA/DFF}}{\texttt{Starting amount of HMF}} \tag{2}$$

2.3 Oxidation procedures

In the catalytic screening experiments performed at ambient air pressure, catalyst (100 mg, 0.025 mmol Ru) and IL (1.0 g) were mixed in a 40 mL tube and stirred at 100-140 ^{o}C for 10 minutes. HMF (70 mg, 0.56 mmol) was added and the mixture was stirred in an open flask for 24 hours. The reaction was subsequently cooled down to room temperature and diluted to 10 mL with 0.1 M NaOH. Finally, the catalyst was filtered off and the resultant solution analyzed by HPLC.

In the high pressure oxidation reactions, catalyst (0.5 g, 0.125 mmol Ru), HMF (350 mg, 2.78 mmol) and IL (12.0 g) were mixed in a Parr autoclave, pressurized with dioxygen (10-30 bar) and stirred at 100-140 ^{o}C for 5 hours. The reaction mixture was cooled down to room temperature and diluted to 100 mL with 0.1 M NaOH. Finally, the catalyst was filtered off and the resultant solution analyzed by HPLC.

2.4 Procedure for leaching test

Catalyst (100 mg, 0.025 mmol Ru) and [EMIm][OAc] (1.0 g) were mixed in a 40 mL tube and stirred at 100 ^{o}C for 3 hours. The catalyst was filtered off affording a black colored liquid. HMF (70 mg, 0.56 mmol) was added to the liquid and the mixture was stirred in an open flask at 100 ^{o}C for 24 hours. The mixture was cooled down to room temperature, diluted to 10 mL with 0.1 M NaOH, filtered and analyzed by HPLC.

3 Results and Discussion

3.1 HMF Oxidation at Ambient Pressure

The ILs best suited for the synthesis of HMF from fructose or glucose have proven to be 1-ethyl-3-methylimidazolium chloride ([EMIm]Cl) and 1-butyl-3-methylimidazolium chloride ([BMIm]Cl).[30] Consequently, [EMIm]Cl was applied for initial screening of catalysts with $Ru(OH)_x$ supported on different carriers for the HMF oxidation at ambient pressure. A relatively high temperature was chosen in order to reduce the impact of viscosity of the mixture formed between the catalyst and IL. Since the screening was performed to allow comparison of the influence induced by the different types of catalyst supports, the reduced solubility of oxygen at elevated temperature was at this stage disregarded. The experiments were performed in open tubes and the results are shown in Table 1.

Table 1. HMF oxidation in [EMIm]Cl with various $Ru(OH)_x$/support catalysts.[a]

		Conversion (%)	Yield (%)		
Entry	Catalyst	HMF	DFF	HMFCA	FDA
1	$Ru(OH)_x/TiO_2$	92	0	1	3
2	$Ru(OH)_x$/spinel	89	0	7	3
3	$Ru(OH)_x/Fe_2O_3$	99	0	14	5
4	$Ru(OH)_x/ZrO_2$	84	0	3	5
5	$Ru(OH)_x/CeO_2$	86	0	7	4
6	$Ru(OH)_x$/HAp	81	0	4	4
7	$Ru(OH)_x$/HT	>99	0	20	5
8	$Ru(OH)_x$/MgO	>99	0	20	2
9	$Ru(OH)_x/La_2O_3$	>99	0	25	1

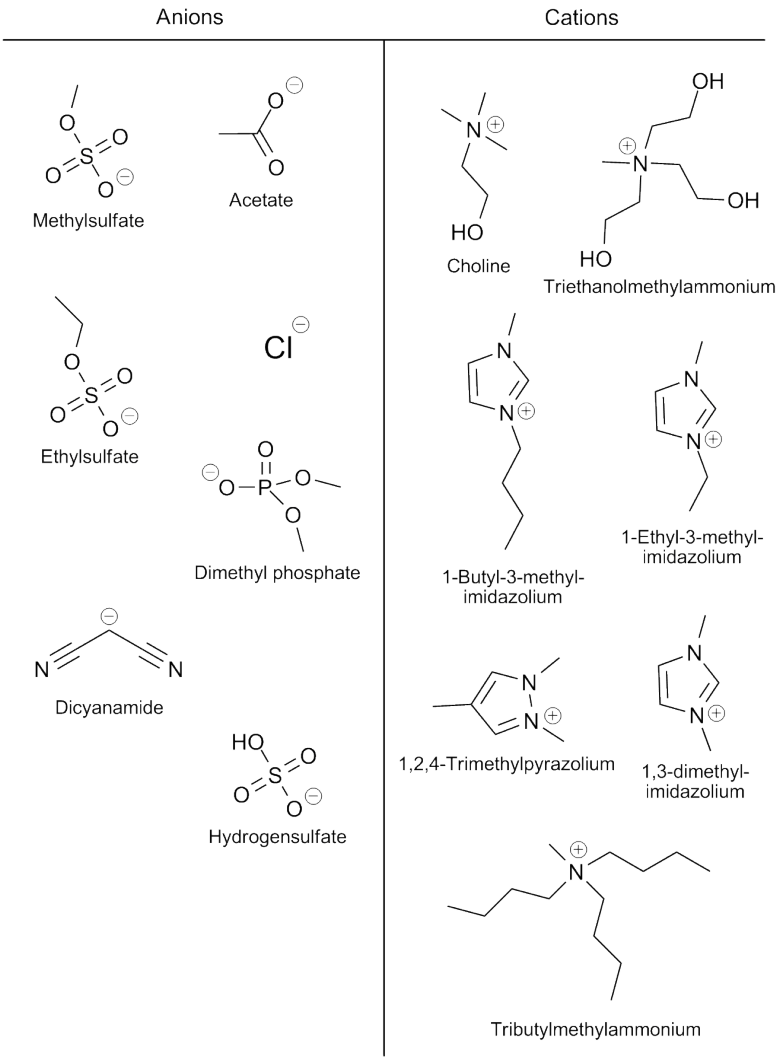
[a] Reaction conditions: 1.0 g [EMIm]Cl, 68 mg (0.54 mmol) HMF, 100 mg catalyst (2.5 wt% Ru, 0.025 mmol), 140 ^{o}C, 24 hours, ambient air pressure.

All catalysts were found to exhibit activity in [EMIm]Cl. Even though the yields of FDA in all cases were low, an indication of which catalysts were the most promising candidates for further study could be derived from the yields of HMFCA. The best catalysts (Table 1, entries 3 and 7-9) were $Ru(OH)_x/Fe_2O_3$, $Ru(OH)_x$/HT, $Ru(OH)_x$/MgO and $Ru(OH)_x/La_2O_3$, which gave yields of HMFCA in the range of 14-25 %. No DFF was observed in any of these experiments.

After oxidation activity had been proven, albeit with low yields, the study was expanded to include other ILs. Notably, the study did not include $[BMIm][BF_4]$ and $[BMIm][PF_6]$ which have been commonly employed in earlier oxidation studies in ILs. These tend to form HF upon contact with moisture at elevated temperature which could be detrimental to reaction intermediates as well as catalyst.[8,33] The ions of the ILs chosen are depicted in Scheme 2.

The most promising catalysts from the first screening were tested together with $Ru(OH)_x/CeO_2$ which had shown superior activity in water.[32] Additionally, the catalyst precursor $RuCl_3$ was included for comparison. Most of the reactions afforded very low yields for the different oxidation products and only a few gave interesting results for further studies. The results for the most interesting ILs are summarized in Table 2 while the complete screening results of all ILs can be found in supporting information (Table S1).

For 1-ethyl-3-methylimidazolium acetate ([EMIm][OAc]) formation of FDA was observed with $Ru(OH)_x/La_2O_3$ and $Ru(OH)_x$/spinel (Table 2, entries 7 and 10). Surprisingly, 6 % of FDA was also formed when using the homogeneous catalyst $RuCl_3$ (entry 9). Formation of HMFCA was also observed for all other catalysts in [EMIm][OAc] indicating that the oxygen solubility was higher compared to other ILs. No solubility data for dioxygen in [EMIm][OAc] was available in literature, but the solubility of O_2 is generally low in comparison to other gases in ILs.[34–38] Another IL that showed promising results was 1-ethyl-3-methylimidazolium hydrogen sulfate ($[EMIm][HSO_4]$) which afforded 19 % FDA using $Ru(OH)_x$/HT (entry 1). When employing $Ru(OH)_x/CeO_2$ in the same IL 9 % of DFF was formed. No other oxidation products were observed along with a slightly lower conversion for HMF compared to $Ru(OH)_x$/HT (entry 3). The cat-



Scheme 2. The cations and anions of the ILs used in the HMF oxidation study.

alyst precursor $RuCl_3$ had no activity in [EMIm][HSO_4] (entry 4). Tributylmethylammonium methylsulfate ([Bu_3MeN][$MeOSO_3$]) and 1,2,4-trimethylpyrazolium methylsulfate ([MMMPz][$MeOSO_3$]) gave DFF formation in combination with $Ru(OH)_x$/spinel. The HMF conversion was much higher in [MMMPz][$MeOSO_3$] with $Ru(OH)_x$/spinel compared to $Ru(OH)_x/La_2O_3$ suggesting that the interaction between the IL and spinel resulted in species that had a detrimental effect on HMF stability (entries 11-13).

Table 2. HMF oxidation in different ILs with various $Ru(OH)_x$/support catalysts.[a]

			Conversion (%)	Yield (%)		
Entry	Ionic liquid	Catalyst	HMF	DFF	HMFCA	FDA
1	[EMIm][HSO_4]	$Ru(OH)_x$/HT	99	1	0	19
2	[EMIm][HSO_4]	$Ru(OH)_x$/spinel	55	3	0	0
3	[EMIm][HSO_4]	$Ru(OH)_x/CeO_2$	77	9	1	0
4	[EMIm][HSO_4]	$RuCl_3$	84	0	0	0
5	[EMIm][HSO_4]	$Ru(OH)_x/La_2O_3$	71	3	0	0
6	[EMIm][OAc]	$Ru(OH)_x$/HT	93	0	13	0
7	[EMIm][OAc]	$Ru(OH)_x$/spinel	99	0	27	13
8	[EMIm][OAc]	$Ru(OH)_x/CeO_2$	55	1	2	0
9	[EMIm][OAc]	$RuCl_3$	>99	0	27	6
10	[EMIm][OAc]	$Ru(OH)_x/La_2O_3$	>99	0	30	10
11	[Bu_3MeN][$MeOSO_3$]	$Ru(OH)_x$/spinel	64	12	0	0
12	[MMMPz][$MeOSO_3$]	$Ru(OH)_x$/spinel	95	6	0	0
13	[MMMPz][$MeOSO_3$]	$Ru(OH)_x/La_2O_3$	46	10	0	0

[a] Reaction conditions: 1.0 g IL, 68 mg (0.54 mmol) HMF, 100 mg catalyst (2.5 wt% Ru, 0.025 mmol), 140 ^oC, 24 hours, ambient air pressure.

In our previous work at high temperature,[39] we have demonstrated that [EMIm][OAc] has a detrimental effect on HMF stability. Accordingly, we investigated the effect of lowering the reaction temperature. Both [EMIm][HSO_4] and [Bu_3MeN][$MeOSO_3$] proved to be very viscous in combination with the catalyst at 100 ^oC, which was why experiments with these liquids were only performed at lower temperature in autoclave with mechanical stirring in the later high-pressure experiments (*vide infra*). In Figure 1 the product distribution for the oxidation of HMF in [EMIm][OAc] with $Ru(OH)_x$/spinel at 100 ^oC is shown as a function of time. The final yield of FDA was lower than in the high-temperature experiments and no DFF was detected, whereas the yield of HMFCA was higher and almost amounted to 50 %. The conversion of HMF remained high, accentuating the need of faster oxidation kinetics to avoid degradation. The best result at 100 ^oC was obtained with La_2O_3 as catalyst support (Figure 2). Here the HMF conversion reached a maximum already after 6 hours which coincided with

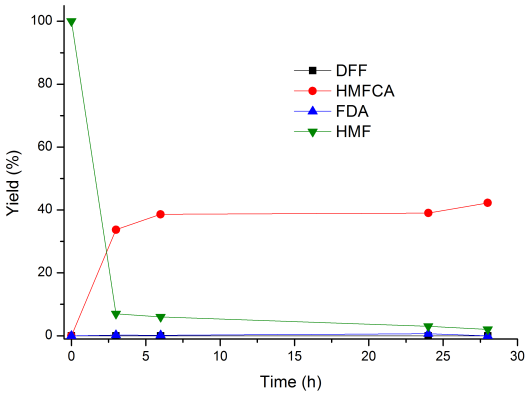


Figure 1. Oxidation of HMF with $Ru(OH)_x$/spinel in [EMIm][OAc] at 100 °C. Reaction conditions: 1.0 g IL, 68 mg (0.54 mmol) HMF, 100 mg catalyst (2.5 wt% Ru, 0.025 mmol), 100 °C, ambient air pressure.

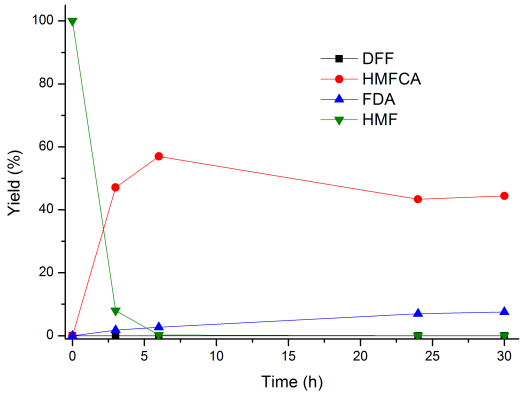


Figure 2. Oxidation of HMF with $Ru(OH)_x/La_2O_3$ in [EMIm][OAc] at 100 °C. Reaction conditions: 1.0 g IL, 68 mg (0.54 mmol) HMF, 100 mg catalyst (2.5 wt% Ru, 0.025 mmol), 100 °C, ambient air pressure.

an HMFCA yield of 58 %. The amount of HMFCA then declined slowly to form FDA which reached a yield of around 10 % after 30 hours.

3.2 HMF Oxidation at High Pressure

The open-flask experiments performed at ambient air pressure showed potential for oxidations at higher pressure. The generally low solubility of molecular oxygen in ILs lead to the assumption that pressures significantly higher than ambient were required

to reach full conversion of HMFCA to FDA. In addition to the oxidation products obtained in the reactions at atmospheric pressure, formic acid (FA) was formed to various extent at higher oxygen pressure. A summary of the results from the high pressure experiments is shown in Table 3.

The first series of autoclave experiments were conducted with 10 bar of dioxygen at

Table 3. HMF oxidation in different ILs with $Ru(OH)_x$/support catalysts.[a]

					Conversion (%)		Yield (%)		
Entry	Ionic liquid	Catalyst	$P\,O_2$ (bar)	T (^oC)	HMF	FA	DFF	HMFCA	FDA
1	$[EMIm][HSO_4]$	$Ru(OH)_x$/spinel	10	140	58	0	3	1	0
2	[EMIm][OAc]	$Ru(OH)_x$/spinel	10	140	>99	0	0	4	14
3	$[EMIm][HSO_4]$	$Ru(OH)_x$/HT	10	100	32	0	18	3	0
4	[EMIm][OAc]	$Ru(OH)_x/La_2O_3$	10	100	97	31	0	34	23
5	$[Bu_3MeN][MeOSO_3]$	$Ru(OH)_x$/HT	30	100	60	0	26	16	1
6	$[Bu_3MeN][MeOSO_3]$	$Ru(OH)_x$/spinel	30	100	62	0	18	26	3
7	$[EMIm][HSO_4]$	$Ru(OH)_x$/HT	30	100	52	0	25	8	0
8	[EMIm][OAc]	$Ru(OH)_x/La_2O_3$	30	100	98	30	0	12	48

[a] Reaction conditions: 12 g IL, 350 mg (2.78 mmol) HMF, 0.5 g catalyst (2.5 wt% Ru, 0.125 mmol), 5 hours.

140 ^{o}C with a reaction time of 5 hours. Using $Ru(OH)_x$/spinel in $[EMIm][HSO_4]$ (Table 3, entry 1) a very similar result to the open flask experiment at ambient pressure was obtained (Table 2, entry 2). Evidently, the increased pressure was in this case insufficient to impose an effect on the slow gas mass transfer. The use of $Ru(OH)_x$/spinel in [EMIm][OAc] resulted in a decrease in HMFCA yield from 27 to 4 %, while the yield of FDA only increased from 13 to 14 % (entry 2). The high temperature in combination with an increased pressure most likely accelerated degradation in [EMIm][OAc], leading to lower yields than at ambient pressure.

In light of the improved results obtained when lowering the reaction temperature for the open flask experiments, high pressure reactions were also conducted at 100 ^{o}C. For $Ru(OH)_x$/HT in $[EMIm][HSO_4]$ this resulted in a significant reduction of HMF conversion from 99 to 32 % and no formation of FDA, whereas HMFCA and DFF were obtained in 3 and 18 % yield, respectively (entry 3). This was most likely a consequence of higher viscosity which made mixing more difficult, resulting in slower gas diffusion and accompanying mass transfer limitations. The same phenomenon appeared in the case of $Ru(OH)_x$/spinel in $[Bu_3MeN][MeOSO_3]$ where the FDA yield was lowered drastically from 10 to 1 %. Improvement was observed at 100 ^{o}C for $Ru(OH)_x/La_2O_3$ in [EMIm][OAc] where 23 % of FDA was formed along with 34 % of HMFCA (entry 4). Clearly, the detrimental effect of [EMIm][OAc] on HMF stability

was reduced and conversion to the desired product was favored when decreasing the temperature.

The final adjustment made was to increase the dioxygen pressure even further to 30 bar. This gave a slight increase in HMF conversion from 32 to 52 % for $Ru(OH)_x$/HT in [EMIm][HSO_4], but still with no FDA being formed (entry 7). The best result was obtained with $Ru(OH)_x/La_2O_3$ in [EMIm][OAc] which afforded an FDA yield of 48 % and an HMFCA yield of 12 % (entry 8). In addition to the desired products, 30 % of FA was formed, suggesting that some oxidative degradation was favored at elevated pressure in [EMIm][OAc].

3.3 Leaching Study

Heterogeneous catalysts can be sensitive to leaching of the active catalytic specie from the support which can be deceptive when interpreting experimental results. The reaction conditions for the performed oxidation experiments were such that leaching was not unlikely, and the experiments using the catalyst precursor $RuCl_3$ at ambient pressure had already confirmed that HMF oxidation could also proceed homogeneously. Accordingly, the two most promising catalysts ($Ru(OH)_x/La_2O_3$ and $Ru(OH)_x$/spinel) were tested toward leaching. This was made by stirring the catalysts in [EMIm][OAc] at 100 ^oC for three hours, after which they were removed by hot filtration. In both cases the resultant liquid received a black color indicating presence of ruthenium. To investigate if the black substance had a catalytic effect, the recovered IL was stirred in an open flask together with HMF for 24 hours. This afforded a substantial amount of HMFCA (44 %) as well as FDA (4 %) confirming that the solid catalysts had leached active catalytic material into the IL. This verified that the catalytic oxidation proceeded, at least partly, homogeneously, thus making direct reuse difficult.

4 Conclusions

The aerobic oxidation of HMF was investigated in various ILs using solid ruthenium hydroxide catalysts supported on different carrier materials. The IL best suited for the

oxidation was [EMIm][OAc] which afforded an FDA yield of 48 % using 30 bar of O_2 at 100 ^{o}C with $Ru(OH)_x$ on La_2O_3 support. The oxidation proved to proceed, at least partly, homogeneously since catalytic activity was found in experiments using an IL from which the catalyst had been filtered off.

An apparent improvement of the yield was found when lowering the temperature and increasing the pressure. Even though [EMIm][OAc] is notorious in degrading HMF[39] and naturally not ideal as solvent for HMF oxidation, it appears to have a higher solubility for oxygen compared to other ILs, which made it the best solvent under the applied reaction conditions. In several ILs the stirring was hampered because of high viscosity which most likely also had an impact on gas mass transfer and consequently on conversion and yield.

We believe that this work provides valuable insights about the scope and limitations of aerobic oxidations in ILs using solid ruthenium hydroxide catalysts. The study also shows that the IL [EMIm][OAc] worked well as solvent for aerobic oxidations making it attractive as reaction media considering its unique dissolving properties. Future work will focus on synthesizing catalysts with higher chemical resistant by alternative preparation methods and investigating other oxidation reactions in [EMIm][OAc] or structurally similar ILs.

5 Acknowledgment

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Assessment of an Ionic Liquid Based Process for the Synthesis of 5-(Hydroxymethyl)furfural from Carbohydrates

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1 Introduction

The future depletion of the world's oil reserves and the increased threat of climate change have intensified research in recent years on fuels and chemicals from renewable resources via so–called biorefineries. One of the most interesting potential platform chemicals that could be produced in a future biorefinery is 5-(hydroxymethyl)furfural (HMF) which may be synthesized via the dehydration of hexose sugars[1,2]

Synthesis of HMF from fructose proceeds readily at elevated temperatures in high-boiling aprotic solvents and is catalyzed by Lewis or Brønsted acids.[3] Product recovery from these solvents is nevertheless difficult due to the high water solubility of HMF.[4] An alternative water-based process is also problematic due to acidic hydrolysis of HMF into formic acid and levulinic acid.[5,6] This problem can be overcome to some extent by the use biphasic liquid - liquid systems, such as water - methyl isobutylketone (MIBK) together with phase modifiers that favor the extraction of HMF into the organic phase.[7] The scientific literature reports many attempts to synthesize HMF, but in spite of the work undertaken none of the methods has led to a commercial process. Furthermore, the current price of fructose hinders a cost competitive process. Indeed, a cheaper feedstock such as glucose would open up an opportunity for a process that could be economically feasible. Indeed, if it were possible to establish a successful synthesis from glucose, other processes using the natural polymers of glucose (such as starch and cellulose) as a feedstock would also become feasible.. The synthesis of HMF from glucose has also been studied but requires the use of special catalysts to afford yields adequate for scale-up.[3,8-11]

In recent years ionic liquids (ILs) have become important in many synthetic schemes as alternative solvents due to their negligible vapor pressure, non-flammability and unique dissolving abilities.[12] Interestingly, the synthesis of HMF from fructose and glucose benefits from certain ILs as reaction media.[13,14] Investigated feed-stocks cover not only fructose and glucose but also sucrose (IIgen et al. 2009; Lima et al. 2009; Hu et al. 2009), starch (Hu et al. 2009; Chun et al. 2010) and cellulose (Binder and Raines 2009; Zhang and Zhao 2010), although reaction yields were not adequate, resulting in significant by-products and unconverted sugars. The dehydration from fructose or glucose show better yields and we have reported in detail on this reaction in a recent review (Ståhlberg et al 2011). For example, the use of solvents like 1-ethyl-3-methylimidazolium chloride ([EMIm]Cl) and 1-butyl-3-methylimidazolium chloride ([BMIm]Cl) together with chromium catalysts provide excellent yields from both fructose and glucose.[8,9] The research on the synthesis of HMF in ILs has attracted considerable attention but these methods have so far only been investigated on a laboratory scale and few examples of the necessary downstream processing or process requirement have been reported.

In this work we have selected an example of HMF synthesis in ILs reported in the literature and use this to examine process feasibility. Using the selected example as a base case we have explored alternatives using different starting feed-stocks and alternative concentrations. Four case studies have been evaluated from the perspective of mass, energy and economic indicators. Such an approach helps evaluate the feasibility of such processes and also identifies future research directions to assist in their eventual implementation.

2. Process Description

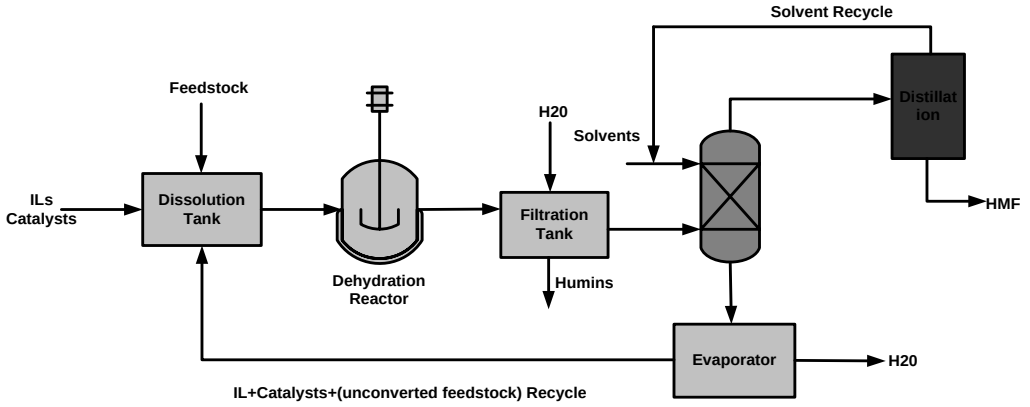


Figure 1. Potential process flowsheet using neat IL as reaction media for the synthesis HMF.[13]

We have published a review paper about synthesis HMF in ionic liquid.[13] In our review paper, we proposed some potential process flowsheets based on what we have summarized in the development of the research work in the synthesis of

HMF in ionic liquids (mainly the reaction development). In this paper, we select one of the published potential flowsheets characterized by using single phase (neat ionic liquid) in dehydration reaction as the base process flowsheet to evaluate the feasibility of synthesis HMF in IL process. The general description of the process flowsheet can be found in the review paper.

In the flowsheet, the feedstock either fructose or glucose is dissolved in the ionic liquid [BMIm]Cl. A homogeneous catalyst (NHC-CrCl2) is used in the dehydration reaction to convert sugar in to HMF. After the dehydration reactor, the produced HMF in the reaction mixture is extracted using ethyl acetate (EtOAc). Due to the high viscosity of IL, water is required to be added prior to extraction. After extraction, the organic phase rich in HMF are sent to a vacuum evaporator to evaporate EtOAc and isolate HMF. Meanwhile, the IL phase together with catalyst, unconverted sugar is sent to the vacuum evaporator to evaporator all the process water added before extraction before recycling back to the dehydration reactor (Figure 1).

3. Materials and methods

3.1. Introduction

The process data (such as reaction yield, temperatures) are the basis for the calculation of mass and energy balance. The flowsheet in Figure 1 is the published conceptual design flowsheet by Ståhlberg et al. (2011) [13], which was proposed based on what was achieved so far in HMF synthesis using ionic liquid. Process data related with all the process units have not been published yet except for the reaction part where most of the research have been placed on. However, other process data such as extraction yield, evaporation temperatures are the necessary data to have in order to calculate the mass and energy so that the process can be evaluated.

For the extraction part, no one has published R_{HMF} between IL and solvent, however that is the base for the extraction calculation. And the extraction process cannot be modeled if R_{HMF} is missing. So we did experiments to measure R_{HMF} between IL and solvent. This experimental value is the basis for simulation of the extraction process and the calculation for mass balance of the downstream. Based on a designed extraction yield (99% HMF), the required number of theoretical stages is calculated with the amount of solvent used for extraction.

Solvent evaporation and IL recovery are simulated in the ProII[15] to get the energy balance. Also since no experimental results related with the mass recovery was published, so we simulated in the modeling to see how much HMF you can actually recovery and calculated the purity.

3.2. Experimental

Extraction experiments were made with 12 different compositions as shown in Table 3. Phase separations of these compositions were investigated at 30, 50 and 70^{o}C. HMF was dissolved in [BMIm]Cl at 70^{o}C in a 100 mL round bottom-flask equipped with a condenser. Water was added and the temperature adjusted to 30 ^{o}C (50 and 70 ^{o}C). EtOAc was added and the biphasic mixture was stirred for 1 hour after which the two phases were left to equilibrate for 1 hour. Samples of 1 mL from each phase were collected and analyzed by HPLC (Agilent 1200 series, Bio-Rad Aminex HPX-87H, 300 mm x 7.8 mm pre-packed column, 0.005 M H_2SO_4 mobile phase, 60 ^{o}C, 0.6 mL/min). The amount of HMF was confirmed by calibration with standard solutions.

Table 3. Composition of HMF, [BMIm]Cl, H_2O and EtOAc in the different experiments.

	1	2	3	4
HMF	0.312 g	0.711 g	1.077 g	4.850 g
[BMIm]Cl	10.0 g	10.0 g	10.0 g	10.0 g
H_20	5, 10 or 20 mL	5, 10 or 20 mL	5, 10 or 20 mL	5, 10 or 20 mL
EtOAc	30 mL	30 mL	30 mL	30 mL

3.3 Mass balance

The basis for the mass balance is an output of 1 kg of final product. The calculation of process inputs (i.e. raw materials, reagents, process aids) and outputs (i.e., products, by-products, waste) were done using standard chemical engineering principles and based on the assumptions of each process units.

Dehydration

The mass balance assumptions for the reaction are taken from published results[8]. Four different reaction options cases are listed for a comparison (see Table 2).

Table 2. Published reaction selectivity to HMF with different choice of feedstock and feed concentration with catalyst amount of 9 mol%, reaction temperature of 100 °C and reaction time of 6 hours.[8]

Case	Feedstock	Feed concentration (wt%)	Selectivity	Conversion
F1	Fructose	17	96	100
F2	Fructose	50	70	100
G1	Glucose	50	81	100
G2	Glucose	50	73	100

Liquid–liquid extractor (LLE)

The extraction process was designed by using a liquid-liquid extractor with designed extraction yield of 0.99 HMF/HMF. The designed extraction solvent volume of EtOAc is 4 times of the volume of IL+H20. For the calculations, equilibrium at each stage was assumed, thus the separation obtained in the extractor is related to the number of theoretical stages and can be calculated by the equations in Perry and Green[16]:

$$\frac{[HMF]_{(IL+H20)in}}{[HMF]_{(IL+H20)out}} = \frac{E^{N_S}(1-E)}{1-E^{N_S+1}} \qquad 2$$

Where $[HMF]_{(IL+H20)in}$ and $[HMF]_{(IL+H20)out}$ are the mole concentration of HMF in the diluted reaction mixture enter and leave the extractor. E is the extraction factor can be calculated as:

$$E = \frac{\rho_{\mathrm{EtOAc}} V_{(IL+H20)in}}{R_{HMF}\rho_{IL+H20} V_{(\mathrm{EtOAc})in}} \qquad 3$$

Where ρ_{EtOAc} and ρ_{IL+H20} are the density of the organic solvent and IL/water mixture and $V_{(\mathrm{EtOAc})in}$ and $V_{(IL+H20)in}$ are the volume of the extraction solvent and IL/water mixture.

Other assumptions hold for the calculation is that both phases must have the same residence time. The parameters in the extraction process are listed in Table 3.

Table 3. Summarized process parameters for second extraction column.

Second extraction	Extraction column
Extraction temperature (°C)	25
Extraction yield (mole HMF_{mibk}/mol $HMF_{aqueous\ in}$)	0.99
Phase feed volume ratio (MIBK/aqueous)	4
R_{HMF}	Experimental results of this work
ρ_{EtOAc} $(\mathrm{kg/m^3})$	897[16]
ρ_{IL+H20} $(\mathrm{kg/m^3})$	1000[17]

HMF Recovery (Solvent Evaporation)

In the unit operation, the designed process is based on the HMF recover yield of 0.99 mol HMF/mol HMF evaporation. We simulated the evaporation process in ProII 8.0[15]. Choosing a temperature at 55 °C, a pressure at 0.1atm, the

simulation result showed that more than 99% HMF can be recovered with less than 1% lost in the vapor phase with EtOAc. The obtained HMF has a purity of 95 wt%. The solvent vapor phase after passing by the condenser and cooling to 50 °C, is recycled back to the extractor again.

IL and Catalyst Recovery (H20 Evaporation)

Qi et al.[18] reported using vacuum oven to dry [BMIm]Cl with Amberlyst resin as catalyst at 60 ◦C for 24 hours and reported 7 times reuse of catalyst and IL. They did not observe any affect of yield during these 7 times reuse. Reusing [BMIm]Cl with HCl as catalyst for 6 times was also reported by Lai and Zhang[19] using vacuum oven at 50 ◦C. They also did not report any affects of yield. In this paper, we chose a vacuum evaporator (with 0.1 atm and 100 ◦C) to ensure all the water can be separated from IL and catalyst at short residence time. The vapor phase after condensing and cooling can be recovered as process water (with small amount EtOAc) and reuse again before extraction.

3.4 Energy balance

The energy required for cooling and heating for each individual unit operation were estimated using typical heat transfer equations. Process temperatures, pressures for estimate heating and cooling enthalpies were based on the process descriptions or conditions for the experiments taken place. The energy balance related with solvent evaporation and condensing was obtained directly from the simulation the process configuration in process simulator PROII[15].

3.5 Economic Evaluation

To access the feasibility of using ionic liquid for HMF production in a large scale, and to compare different reaction options (case F1, F2, G1 and G2), the economic analysis was performed. The economic analysis took into account the cost of the main units of the process (reactor, filter, extractor and evaporators) which is the base for the estimation of the total capital investment, main raw material (glucose/fructose, solvent, [BMIm]Cl and catalyst), utilities costs for the operation of the main units (energy and cooling water), the required labor cost and other expenses (such like plant overhead cost et al.) . The designed plant has a capacity of 25,000 tons/year with 350 working days /year. The location is assumed in US and with the easy access to the raw material and energy supply therefore the transportation of raw material supply was not considered in this analysis.

Estimation of total capital investment (TCI)

With the designed capacity of the plant, and mass balance of the flowsheet, the size of equipments required in the flowsheet was estimated with the residence time of each unit. Sizing, selection and design calculation of the equipments was calculated according to Perry and Green[15]. The cost of purchase the equipments was estimated according to Peters et al. [20] and www.matche.com.[21]

The capital cost includes fixed capital investment (FCI) and working capital investment (WCI). Fixed capital cost (FCI) was calculated with an assumed percentage of total main unit cost[20] (equation 4 and 5).

$$TCI = FCI + WCI \quad (4)$$

$$FCI = E\sum(1 + f_1 + f_2 + f_3 + \ldots + f_n) \quad (5)$$

Where f_1, f_2, …, f_n are multiplying factors for piping, electrical, engineering and supervision etc. The detail the values used for estimation the total investment is listed in Table A1 in the appendix. Total capital investment was calculated based on the assumption that the fixed capital investment is 85% of TCI and the working capital is 15% of TCI.[20]

Estimation of total production cost

The total production cost (TPC) consists of the variable production cost, fixed charges, plant overhead costs and general expenses. The variable production cost includes raw material cost, catalysts and solvents cost, utilities (electricity, steam, process water and cooling water etc.), waste disposal cost, labor and labor supervision cost, plant maintenance and repair cost, operating supplies, laboratory charges, royalties and patent cost. The fixed charges include the taxes of the property, financing, rent, insurance and depreciation charge. Plant overhead cost is the cost directly related to the production operation.

The costs of raw material, solvent, catalysts, utilities and waste disposal were directly related with the mass and energy balance of the designed process. Labor requirements were estimated from the designed equipments in the plant using the method from Peter et al.[20] Other remaining variable costs, fixed cost without depreciation, plant overhead cost and general expenses were estimated with using typical percentage values.[20] The detailed lists with all the costs considered and the percentage used are listed in Table A2 in the appendix. The depreciation was calculated with a constant yearly depreciation rate based on a 10 year schedule.

4. Results

4.1. Introduction

4.2. Experimental determination of partition coefficient

In our experiments, we found out the partition coefficient R_{HMF} is more affected by the composition of IL+ H_20 phase. By adding water into ionic liquid decreasing the viscosity of [BMIm]Cl and thus increase the R_{HMF} (Figure 2). By decreasing the extraction temperature, the R_{HMF} is also slightly increased. However, the effect of the dilution ratio with water showed more significant effect on the R_{HMF}. Although increasing the ratio of water/IL leads to increase the partition coefficient, the dilution will lead to energy consumption to dry the IL before recycle back. Since the energy for evaporate water (boiling point 100 °C) is higher than that for EtOAc (boiling point 77.1 °C), it is better to use less water in dilution and more solvent for extraction process. Therefore, we selected to add the equal amount volume of water into IL(water/IL volume ratio = 1). We chose the exaction temperature as 50 °C. Although R_{HMF} at 30°C is slightly higher, considering the required energy related with temperature change (cooling for extraction and heating for evaporation), we selected the comprise temperature.

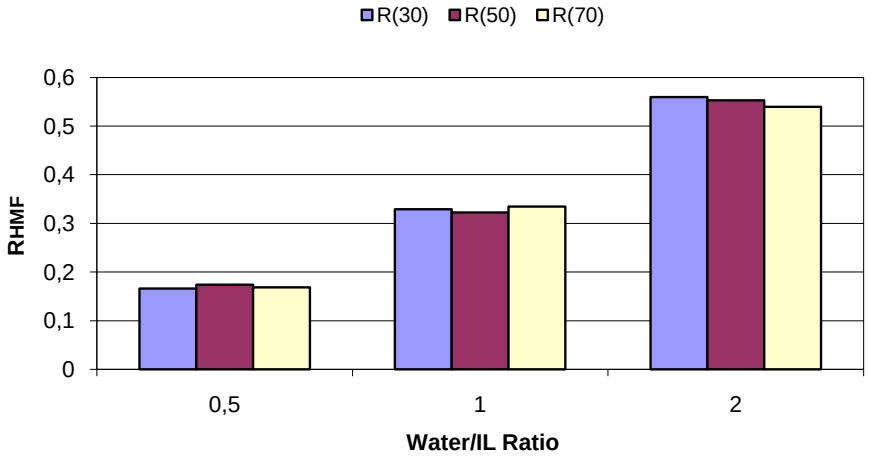


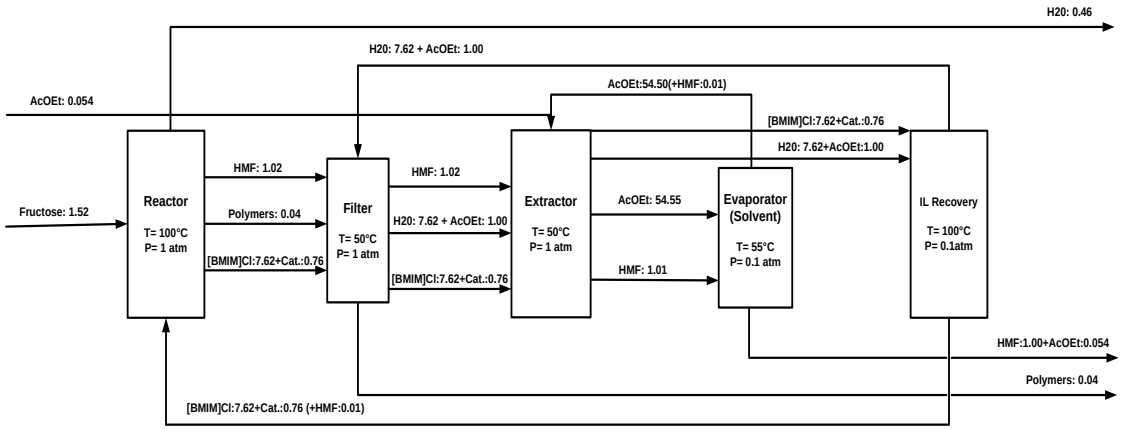
Figure 2. Effects of the water/IL volume ratio and temperature on the partition coefficient.

4.3 Mass Balance

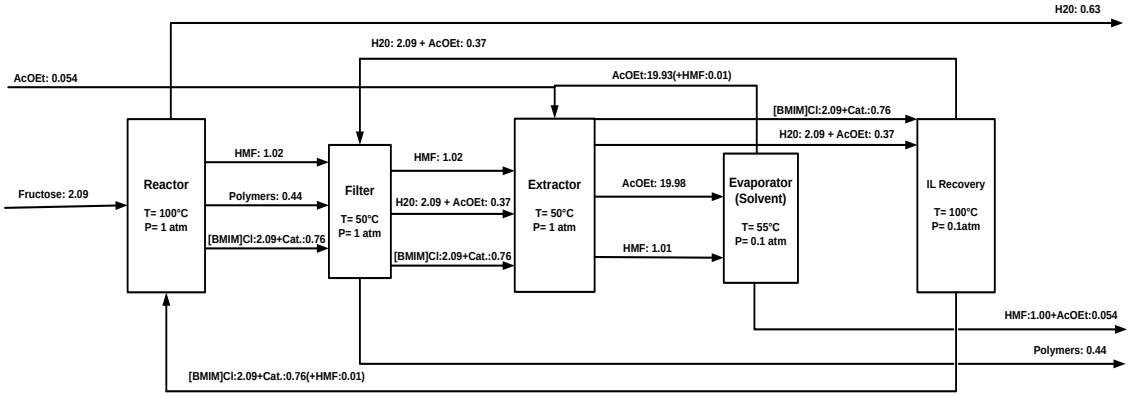
The mass balance results for 1 kg HMF output of the four reaction options are plotted in Figure 3. From the mass balance result, it can be seen that for both cases started with low concentration requires less reactant (fructose/glucose) than for cases with high concentration due to the lower selectivity to HMF in

higher concentration. As a consequence, the byproducts (humins) and formed water from reaction options with low feed concentration are also less for reaction options with high feed concentration. It is always believed that glucose is converted first to fructose, and afterwards to HMF[9,13]. Consequently, the reaction condition is harder and always associated with lower selectivity to HMF and more byproducts (mainly humins) formation (Plot a and Plot c, Figure 3). Interestingly, the selectivity to HMF was more affected by the initial feed concentration for fructose than for glucose (Table 2). At the concentration of 50 wt%, the selectivity to HMF from glucose (73%) is better than from fructose (70%). This gives a less sugar requirement with Case G2 than Case F2 (Plot b and Plot d, Figure 3).

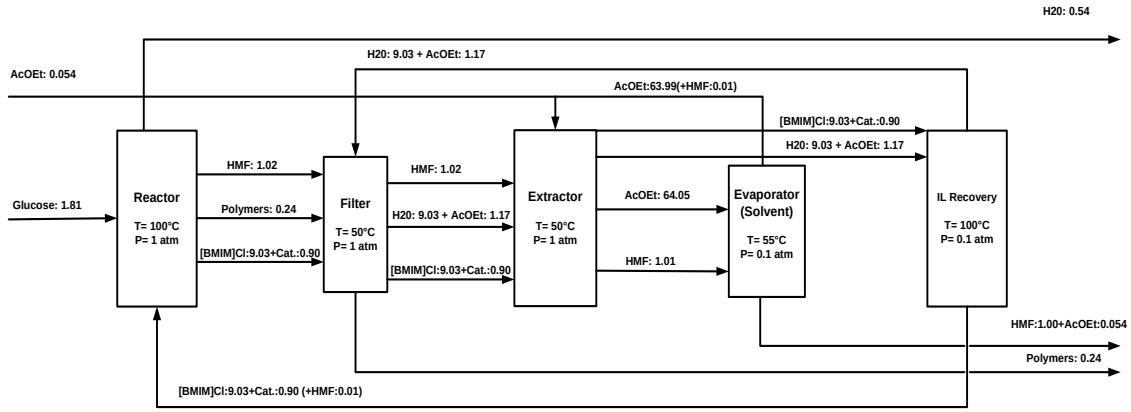
Although using the low concentration feed shows more efficient use of reactant (less byproducts), the disadvantage with low concentration processes is large dilution which requires more reaction medium, solvent and process water in the whole production process. For example, it requires 7.62 kg [BMIm]Cl /kg HMF and 55.55 kg EtOAc /kg HMF respectively in process of fructose with feed concentration of 17wt%. On the other hand, the required amount of [BMIm]Cl is only 2.09 kg/kg HMF and the amount of EtOAc is 20.35 kg/kg HMF for the process of fructose with a feed concentration 50 wt% .



b)


H20: 0.63
H20: 2.09 + AcOEt: 0.37
AcOEt: 0.054
AcOEt:19.93(+HMF:0.01)
[BMIM]Cl:2.09+Cat.:0.76
H20: 2.09 + AcOEt: 0.37
Fructose: 2.09
Reactor
T= 100°C
P= 1 atm
HMF: 1.02
Polymers: 0.44
[BMIM]Cl:2.09+Cat.:0.76
Filter
T= 50°C
P= 1 atm
HMF: 1.02
H20: 2.09 + AcOEt: 0.37
[BMIM]Cl:2.09+Cat.:0.76
Extractor
T= 50°C
P= 1 atm
AcOEt: 19.98
HMF: 1.01
Evaporator
(Solvent)
T= 55°C
P= 0.1 atm
IL Recovery
T= 100°C
P= 0.1atm
HMF:1.00+AcOEt:0.054
Polymers: 0.44
[BMIM]Cl:2.09+Cat.:0.76(+HMF:0.01)

c)


H20: 0.54
H20: 9.03 + AcOEt: 1.17
AcOEt: 0.054
AcOEt:63.99(+HMF:0.01)
[BMIM]Cl:9.03+Cat.:0.90
H20: 9.03 + AcOEt: 1.17
Glucose: 1.81
Reactor
T= 100°C
P= 1 atm
HMF: 1.02
Polymers: 0.24
[BMIM]Cl:9.03+Cat.:0.90
Filter
T= 50°C
P= 1 atm
HMF: 1.02
H20: 9.03 + AcOEt: 1.17
[BMIM]Cl:9.03+Cat.:0.90
Extractor
T= 50°C
P= 1 atm
AcOEt: 64.05
HMF: 1.01
Evaporator
(Solvent)
T= 55°C
P= 0.1 atm
IL Recovery
T= 100°C
P= 0.1 atm
HMF:1.00+AcOEt:0.054
Polymers: 0.24
[BMIM]Cl:9.03+Cat.:0.90 (+HMF:0.01)

d)

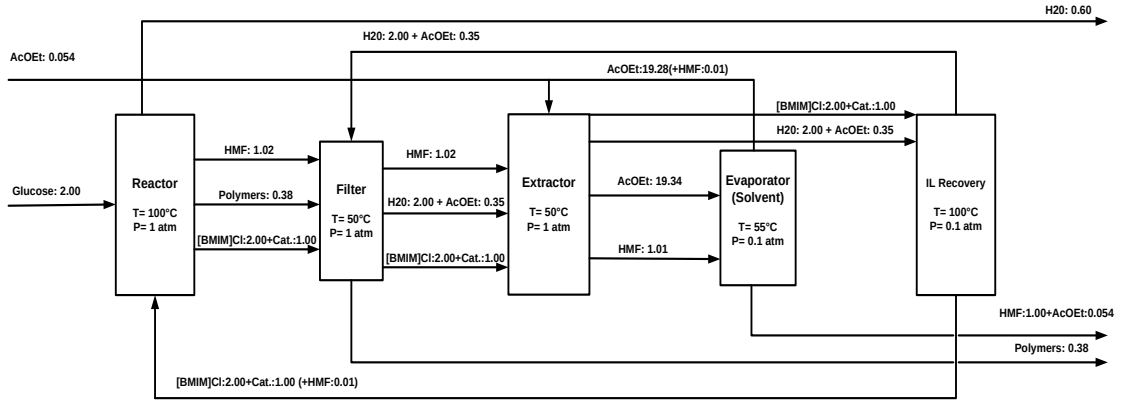

H20: 0.60
H20: 2.00 + AcOEt: 0.35
AcOEt: 0.054
AcOEt:19.28(+HMF:0.01)
[BMIM]Cl:2.00+Cat.:1.00
H20: 2.00 + AcOEt: 0.35
Glucose: 2.00
Reactor
T= 100°C
P= 1 atm
HMF: 1.02
Polymers: 0.38
[BMIM]Cl:2.00+Cat.:1.00
Filter
T= 50°C
P= 1 atm
HMF: 1.02
H20: 2.00 + AcOEt: 0.35
[BMIM]Cl:2.00+Cat.:1.00
Extractor
T= 50°C
P= 1 atm
AcOEt: 19.34
HMF: 1.01
Evaporator
(Solvent)
T= 55°C
P= 0.1 atm
IL Recovery
T= 100°C
P= 0.1 atm
HMF:1.00+AcOEt:0.054
Polymers: 0.38
[BMIM]Cl:2.00+Cat.:1.00 (+HMF:0.01)

Figure 3. Block scheme diagram of mass flow balance for 1 kg HMF production of different processes. plot a) is for process starting with an initial fructose concentration of 17 wt% (F1), plot b) is for process starting with an initial fructose concentration of 50 wt% (F2), plot c) is for process starting with an initial glucose concentration of 17 wt% (G1) and plot d) is for process starting with an initial glucose concentration of 50 wt% (G2).

4.2 Energy Balance

The energy balance result for the four reaction options were plotted in Figure 4. The calculated energy requirement for major process units are listed in Table A3 (Appendix). The difference for energy requirements between high concentration feed and low concentration feed for both glucose and fructose are significant. High dilution leads to high energy consumption to recover the reaction medium, process water and solvent. The total energy consumption for process with feed concentration of 17wt% fructose is 85 MJ/kg HMF which is 2.7 times of that required for process with feed concentration of 50 wt% fructose. The energy consumption of process with feed concentration of 17 wt% glucose (101 MJ/kg HMF) is also around 3.3 times of the energy required for process with feed concentration of 50 wt% glucose (30 MJ/kg HMF).

From the energy distribution of the four cases, the largest energy consumption is the energy for condensing (over 40% of the total energy). The calculated condensing energy here is the sum of the energy to condense the vapor solvent and the energy to condense the vapor process water. Considering the large amount of solvent used in the extraction process in order to reach an efficient extraction due to the low partition coefficient of HMF, the energy for evaporating solvent and condensing the solvent before recycling are therefore significant. Other major energy consumptions after condensing are the energy for EtOAc evaporation and followed by the energy for IL recovery (process water evaporation).

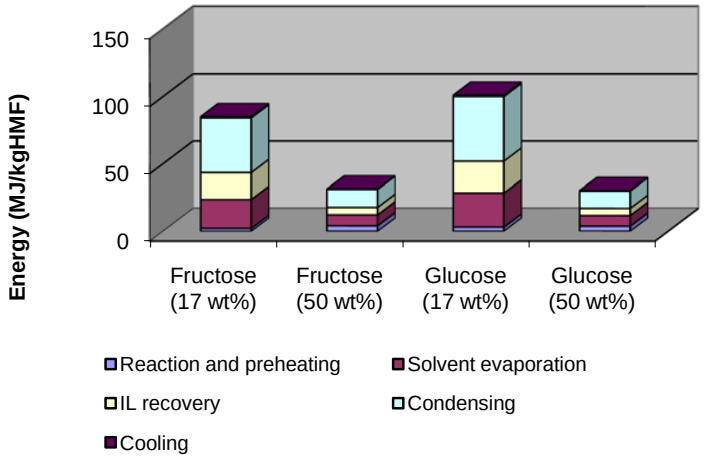


Figure 4. Plot of the required energy for the major process units in the process flowsheets for the four process options.

4.3 Equipment Sizing

The calculated size and capacity of the major equipments involved in the process flowsheet of the four cases are listed in Table 4. Due to the dilution with the low concentration feed, the required volume for all the equipments for process options F1 and G1 are around 2 to 3 times of that for process options F2 and G2. The heat exchanger 1 is used to provide heat for reaction. The heat exchanger 2 and exchanger 3 are used to condense the vapor solvent and process water vapor, respectively. Since the required energy amount for condensing both solvent and water are large, the required areas for both heat exchangers are also large. The required reactor volume was calculated with residence time of 6 hours. Since the reaction was not optimized yet, there is space to reduce the residence time and the required volume of reactor can consequently be reduced.

Table 1. Calculated capacity of major equipment of the designed capacity for the four process options.

	F1	F2	G1	G2
Reactor Volume (m3)	178	94	212	90
Filter Capacity (m3)	29	11	34	11
Extractor Diameter (m)	1.4	2.3	2.5	1.4
Trays number	30	31	31	30
Total Extractor Height (m)	23	24	24	23
Vacuum Evaporator 1 (m3)	30	11	35	11
Vacuum Evaporator 2 (m3)	3.8	1.4	4.5	1.4
Heat Exchanger 1 Area (m2)	11	3	12	3
Heat Exchanger 2 Area (m2)	833	305	980	296
Heat Exchanger 3 Area (m2)	620	177	737	170

4.3 Economic Analysis

The economic analysis was done to compare and evaluate different process options for HMF productions using IL and to access the economic feasibility of the process options. The total capital investment was calculated by using percentage of delivered major equipment (Table 4) cost as described in the methodology part. The calculated total capital investment for different process options were listed in Table 5. The capital investment is highly related with the required capacity of the equipments. Low feed concentration cases like (F1 and G1) have much higher capital cost than that for high feed concentration cases (F2 and G2). The total capital investment for the cases with the same feed concentration is similar.

Table 2. Total capital investment for HMF IL process options.

Item	Cost (Million USD)			
	F1	F2	G1	G2
Total direct plant cost[a]	7.5	4.6	8.4	4.5
Total indirect plant cost[b]	3.1	1.9	3.5	1.9
Fixed capital investment (85% TCI)	10.6	6.5	11.9	6.4
Working capital (15% TCI)	1.8	1,2	.2.1	1.1
Total Capital Investment	12.5	7,7	14.0	7.6

a)Includes: Purchased equipment (PE), installation equipment (39%PE), instrumentation(43%PE), Piping (31%PE), electrical (10%PE), yard improvement (15%PE) and service facilities (55%PE).
b)Includes; engineering and supervision (32%PE), construction expense (34%PE), legal expense (4%PE), contractor fee (19%PE) and contingency (37%PE).

The calculated production cost of HMF consists of variable cost (mainly the material cost, utility cost, labor cost and maintenance cost), fixed cost (tax, insurance and depreciation), plant overhead cost and general expense. A detailed percentage used for calculation with all the cost considered in the HMF production cost can be found in Appendix. The depreciation cost is calculated as 10% of total capital investment per year (assuming a recovery period of 10 years). The calculated HMF production cost without adding the cost of IL and catalyst for the examined four cases are listed in Table 6.

The HMF production cost for cases with glucose as feedstock (G1 and G2) is cheaper than that for cases start with fructose (F1 and F2). The lowest HMF production cost without considering IL and catalyst cost is G2 with high glucose feed concentration (1.12 USD/kg HMF). The highest production cost was obtained with F2 with high fructose feed concentration (1.62 USD/kg HMF). For all the four cases, the cost of reactant (glucose/fructose) dominated the whole production cost, followed by the cost of utilities (heating steam and cooling water)

when the cost of IL + catalyst is not considered (Figure 5). The fixed cost and other variable cost which both related with total capital investment cover the whole HMF production cost around 7 to 11% for all four process options. This indicates the effect of the total capital investment to the HMF production cost is not significant. This effect can be further decreased by increasing the production scale. The major HMF production cost (without IL+ Catalyst cost) still comes from the cost of the reactant and utilities for all the four cases. The cost of utilities for processes with low feed concentration (F1 and F2) is around 3 times of that for processes with high feed concentration (F2 and G2). However, the decreasing selectivity with high feed concentration increases the required amount of reactant which consequently increases the cost of reactant. For processes starting from glucose, the decreased utilities cost with increased feed concentration is bigger than the increased cost of reactant. Therefore, the HMF production cost of G2 is lower than that of G1. On the other hand, for processes with fructose as feed, the save energy cost with a higher feed concentration (F2) cannot pay back the cost of lost of fructose due to a high fructose cost.

Table 3. HMF production cost without adding IL and catalyst cost for four process options.

Item	HMF production cost (USD/kg HMF)				
		F1	F2	G1	G2
Material cost	Glucose/Fructose	0.76	1.04	0.54	0.60
	Solvent	0.05	0.05	0.05	0.05
Utilities	Steam (MP 200 Pigs)	0.31	0.13	0.37	0.12
	Cooling water	0.03	0.01	0.03	0.01
Labor and Labor supervision		0.08	0.08	0.08	0.08
Other variable cost		0.11	0.10	0.10	0.07
Fixed cost		0.06	0.04	0.07	0.04
Plant overhead cost		0.06	0.05	0.06	0.05
General expense		0.12	0.13	0.11	0.09
Total		1.58	1.62	1.42	1.12

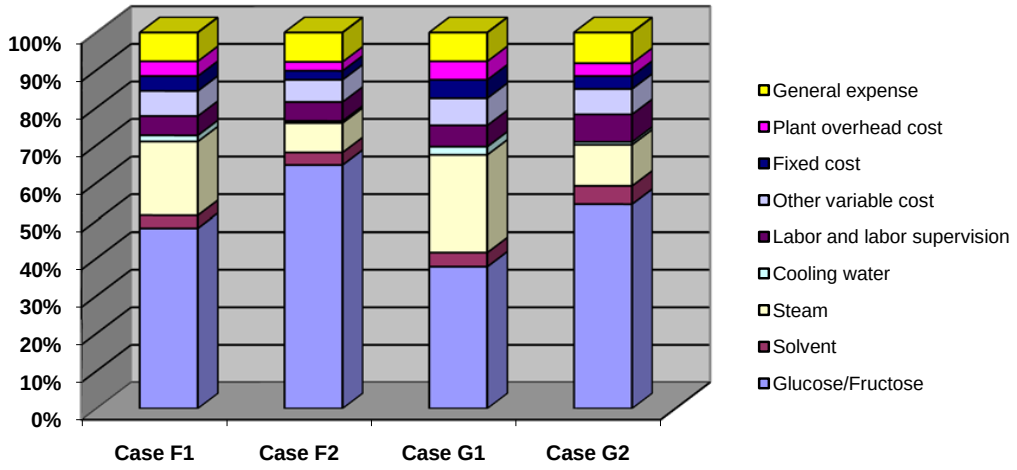


Figure 5. Cost distribution for HMF production cost without adding IL + Catalyst cost.

5. Discussion

5.1 IL + Catalyst reuse times

The required amount of IL and catalyst amount for HMF production (which is the base for calculation of the cost of IL+ catalyst for HMF production) is highly depended on how many times IL+ catalyst can be reused. Successfully reuse [BMIm]Cl +catalyst for 6 or 7 times without affecting any selectivity of HMF production have been reported [18,19]. However, for large scale production, 6 or 7 times reuse is far away from enough due to a high cost of IL. If the cost of [BMIm]Cl is 11USD/kg and the catalyst is 2 USD/kg, the effect of reuse times of IL+ catalyst to HMF production cost is plotted in Figure 6 for the four cases. In Figure 6, the HMF production cost is highly affected by the reuse times of IL system. The reuse time here is assumed as the times that IL and catalyst can be reuse for HMF production without affect the selectivity. The HMF production cost decreased dramatically with the reuse times of IL+ catalyst until the reuse time reaches 50. After 50 times of reusing IL and catalyst, the HMF production cost for processes with high feed concentration (G2 and F2) becomes reducing slowly with the recycle times. After recycling 150 times of IL+ catalyst, the effect of recycling time to HMF production cost is not significant anymore. The cost of sugar starts to dominate on HMF production cost again. If the IL+ catalyst can be reuse for around 200 times without significant affect on the selectivity of HMF production from sugar, the HMF production cost for F1, F2, G1 and G2 is around 1.97 USD/kg HMF, 1.74 USD/kg HMF, 1.88 USD/kg HMF and 1.23 USD/kg HMF, respectively. Clearly, when considering the IL and catalyst cost, processes with high feed concentration are more competitive than process with low feed concentration. This advantage decreases with the increase IL and catalyst reuse times (Figure 6).

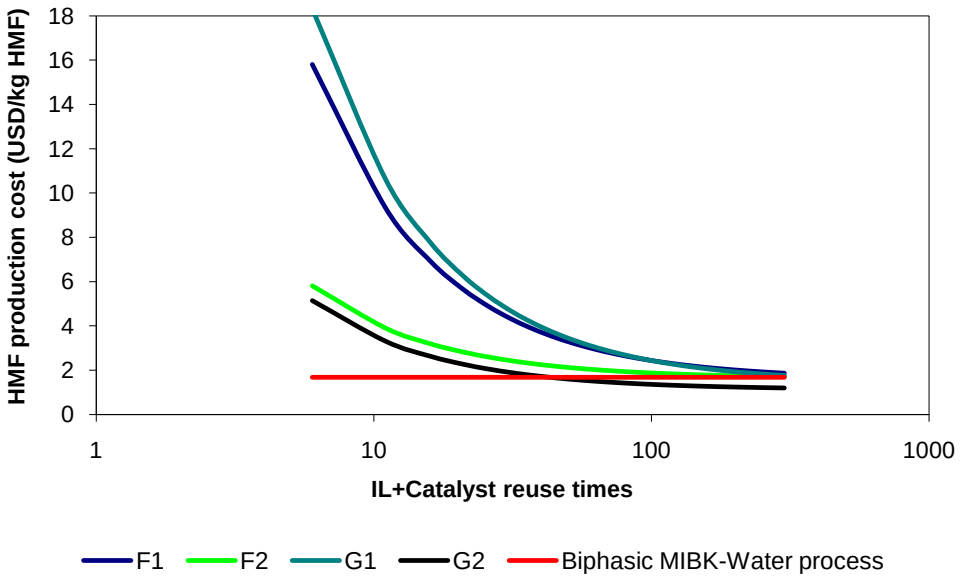


Figure 6. HMF production cost versus. IL+ catalyst reuse times.

5.2 Comparison with Biphasic HMF production process

Besides using IL as reaction medium for HMF production from sugar, HMF can also be produced from fructose in water[22], neat high boiling point solvent such like DMSO [22-26], one phase water-solvent mixture [27-29] and biphasic water-solvent mixture[7,30]. Due to the low selectivity in water as medium, and no industry interest in DMSO as reaction medium for HMF production, using biphasic reaction radium such as water-MIBK with addition of salt or phase modifier appears to be one of the most promising processes for HMF production from fructose [7, 30-33]. The HMF production cost by using MIBK-water as reaction medium, HCl as catalyst with addition of salt (NaCl) was also calculated.

The biphasic MIBK-water process flowsheet is outlined in Figure 7. The aqueous feed to the biphasic reactor consists of fructose and water. The feed concentration is around 30wt% fructose (on a wet weight basis). Hydrochloric acid is added into the aqueous solution as a catalyst with a concentration around 0.25 mol/L. The aqueous phase is saturated with salt (around 35 wt% based on water) to improve the partition coefficient of HMF between water and MIBK[31]. The mixture is heated up and maintained at around 180 °C for 3 minutes. The selectivity for the dehydration of fructose to HMF is 77% (mol HMF/mol Fructose), with a 72% conversion (mol HMF/mol Fructose). Afterwards, the reaction mixture was cooled down to room temperature for the phase separation. The aqueous phase is then sent to a liquid-liquid extractor for the second extraction to remove the leftover HMF in aqueous phase. 99% of HMF can be recovered in this way. Afterwards the aqueous rich in fructose will be recycled back after stripped off the excess water produced in dehydration reaction. Organic phase both form the biphasic reactor and the second extractor will be sent for vacuum evaporation. Based on the simulation results in ProII [15] at 0.01 atm and 314 K, 99.8% of the

MIBK solvent can be recovered in this way with a 1.6% loss of HMF. The total distillation yield for HMF is 98.4% and the purity of obtained HMF is around 95 wt%.

The calculated total capital investment for biphasic process is around 13.5 million USD (detailed equipment sizing, costing can be found in the appendix), which is higher than the calculated capital investment for IL processes with high feed concentration (F2 and G2) and IL process with low feed fructose concentration. The required dehydration reactor size is around 6 m3 which is much smaller than that calculated for IL processes due to a short residence time (3 minutes) and a high feed concentration (30 wt%). However, since the reactor is high pressurized, the equipment cost is also high. Besides, since the required reaction temperature is quite high, the required total area for heat exchangers is also much bigger than that for IL processes. The calculation for HMF production cost with biphasic process is listed in Table 7. The production cost for HMF by biphasic route is around 1.68 USD/kg HMF.

The HMF production cost by biphasic route was also plotted in Figure 6 (red line). Using IL processes for HMF production, only the process start with glucose with a high concentration (G2) is competitive to the biphasic route with the assumption if the IL system can be reused for around 45 times. Clearly, the more times that IL system can be reused, the HMF production cost by IL process is more close to the cost by biphasic production. The production cost for case G2 starts to be lower after IL reuse times reaches 45 times. However, as it can be seen in Figure 6, besides G2, none of the other three IL processes are able to reach a lower HMF production cost than the biphasic process even if the IL recycle time reaches 300. The dominate factor in HMF production cost by biphasic system is the sugar cost (0.94 USD/kg HMF) which is bigger than that for IL process options F1, G1 and G2. The second biggest part is the cost of the utilities (0.21 USD/kg HMF) which is bigger than that of IL processes with high feed concentrations (F2 and G2) but smaller than that of IL processes with low feed concentrations.

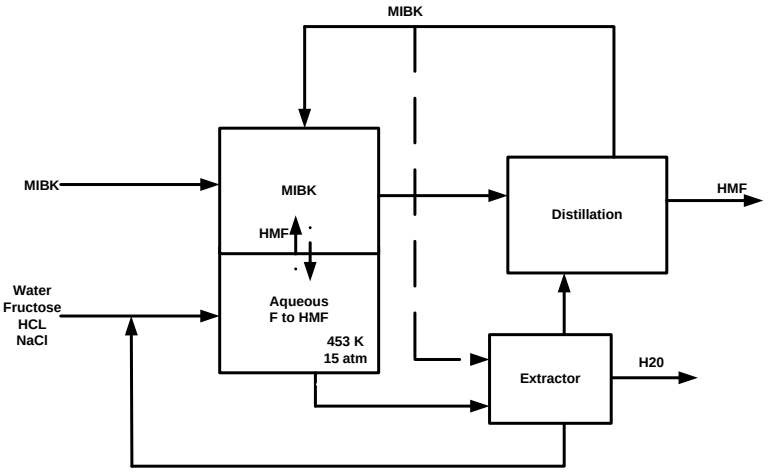


Figure 7. Process flowsheet of dehydration fructose in biphasic reactor (MIBK-water), Modified from Roman-Leshkov et al.[30]

Table 4. Calculated HMF production cost for biphasic process (MIBK-water) for HMF production.

Item		(USD/kg HMF)	Percentage (%)
Material Cost	Fructose	0.94	56.24
	Solvent	0.08	4.76
Utilities	Electricity	0.00	0.04
	Steam	0.19	11.56
	Cooling water	0.01	0.79
Labor	Labor and supervision	0.08	4.85
Other variable cost		0.11	6.71
Fixed cost	Tax, depreciation, insurance	0.07	4.04
Plant overhead		0.06	3.39
General expense		0.13	7.62
HMF total production cost		1.68	100.00

5.3 Improvement for Process Option G2

The cost distribution chat of the HMF production cost using IL process option G2 with the IL and catalyst recycle for 200 times is shown in Figure 8. The glucose cost covers 48%, followed by cost of utilities (steam and cooling water) which is 11%. The cost of IL and catalyst together is around 10%. Other cost related with capital investment is the sum of other variable cost (maintenance, repair and laboratory) and fixed cost, which all together covers around 9%. Since the whole

process is still based on some lab unit operation results, there is still a lot of room for further improvement.

For example, the reaction residence time is based on a bath reaction with 6 hours leading to reactor volume of 90 m^3. On the other hand, the reaction volume required for the biphasic process is only 6 m^3. These of course with further understand the kinetics of the decomposition sugar inside IL, the reaction conditions can be then optimized and reduced the investment cost. The IL cost used for calculation is around 11 USD/kg. In the future, with the demanding scale, the cost may reduce. It then demands less recycling times if IL's price is cheaper. However, based on the price now, recycling more than 46 times is required to be competitive to the biphasic process. The cost can be even more appealing if more than 200 reuse times can be reached. The reaction selectivity for the calculation is chosen as 73%. In the future, this can be further improved. Figure 8 shows the HMF production cost decreasing with the increased dehydration reaction yield (selectivity). If the yield (selectivity) is able to reach 93%, the HMF production cost can reduce to 1 USD/kg HMF. In the large scale production, the process may run in a continuous mode due to the advantages[13]. In the continuous process, the reaction yield would thus equal to the selectivity when the unconverted sugar is fully recycled. This offers great potential for the dehydration glucose to reach the selectivity of 93 %. Of course, this requires further understanding of the reaction kinetics.

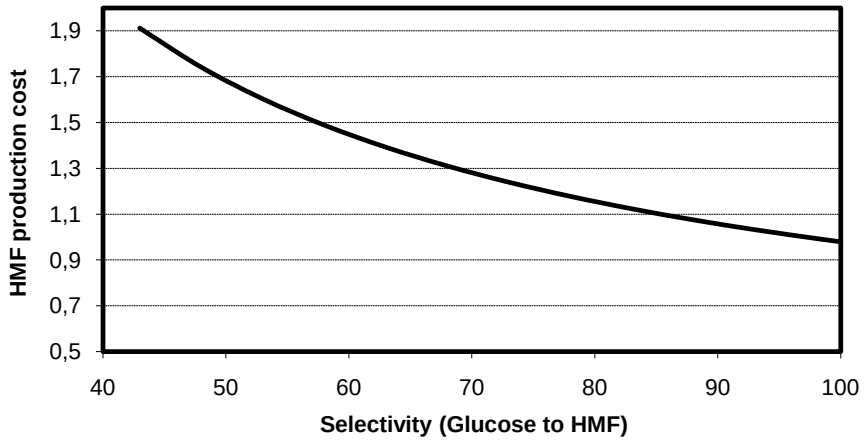


Figure 8. The HMF production cost as a function of the selectivity of the dehydration reaction.

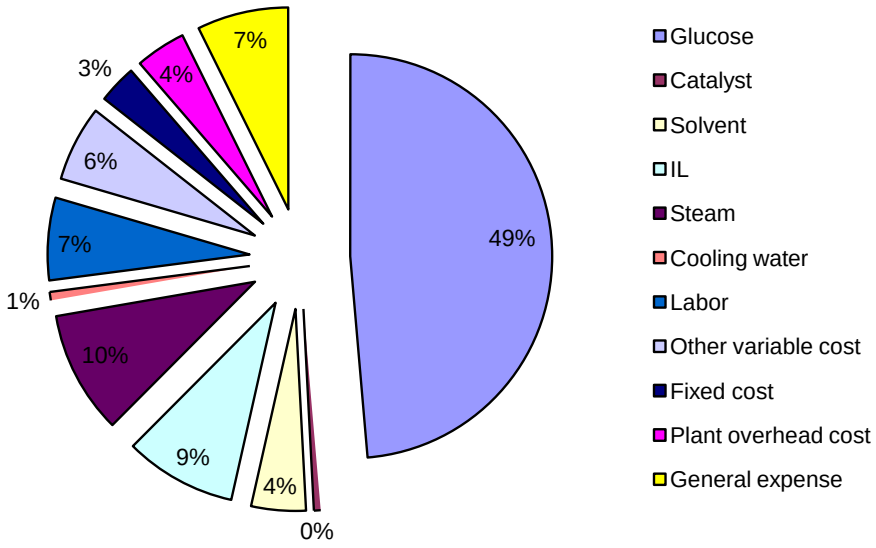


Figure 9. Total HMF production cost breakdown. The production cost is obtained by using the IL process option G2 with an IL and catalyst recycle of 200 times.

6. Conclusions

Using IL for HMF production with different process options starting from fructose and glucose with different initial concentrations were evaluated in this study. Mass and energy balance were done for the four examined cases. The HMF production costs of the four cases were also calculated. The HMF production cost is highly affected by the reuse times of IL and catalyst system. Processes with a high feed concentration show better economic potential than processes with a low feed concentration. IL Processes starting from fructose are more costly than IL processes starting from glucose due to the high cost of fructose.

Using IL processes for HMF production with a high feed glucose concentration with IL and catalyst recycle at least 46 times, can be competitive with the biphasic processes proposed by Roman-Leshkov et al. [30,31] which has a production cost of 1.68 USD/kg HMF in this study.

In the future, in order to realize the HMF production in a large industrial scale, investigations should be placed on investigating the recycle and reuse times of IL and using cheap starting material such as glucose for HMF production. Although the recovery and recycle of ILs together with catalysts have been investigated, the reported recycle time is only around 6 or 7 times which is far away from the requirement for industrial scale up. High concentration feed of glucose showed the best economic potential. The recent research in using IL for synthesis HMF is always using very low feed concentration. In the future, researches should put more emphasis on understanding better the kinetic of

decomposing sugar in IL to be able to maintain a good selectivity even with a high concentration feed.

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Appendix

Table A-1. Typical percentage values for estimation capital investment based on delivered-equipment cost. Values are taken from Peters et al.[20].

Fixed capital investment (FCI)	Percentage of Purchased Equipment
Purchased equipment (delivered, E)	100%
Installation	25-55%
Instrumentation (installed)	8-50%
Piping(installed)	16-68%
Electrical (installed)	15-30%
Building (including service)	5-68%
Yard improvement	10-20%
Service Facilities (installed)	30-80%
Engineering and supervision	32-33%
Construction expenses	34-41%
Legal expenses	4%
Contractor's fee	17-22%
Contingency	35-44%

Table A-2. Typical percentage values for estimation total production cost. Values are taken from Peters et al.[20].

	Type of expenses	Typical values
Variable cost (some)	Labor supervision	15% of the labor cost
	Maintenance and repair	2-10% of fixed capital investment
	Operating supplies	15% of maintenance and repairs
	Laboratory charges	10-20% of the labor cost
	Royalties	0-6% of total production cost
Fixed cost (without depreciation)	Taxes (Property)	1-2% of fixed capital investment
	Financing	5-10% total borrowed capital
	Rent	8-12 percent of total rented property
	Insurance	1% of the fixed capital investment
Plant overhead cost	Plant overhead cost	50-70% of the total labor, supervision and maintenance cost
General expense	Administrative cost	15-25% of operating labor

	Distribution & marketing cost	2-20% of total product cost
	Research & development cost	5% of total product cost

Table A-3 Detailed energy balance data of four case options (MJ/kg HMF).

	F1	F2	G1	G2
Reaction and preheating	2.20	4.13	3.17	3.85
Solvent evaporation	21.40	8.10	25.18	7.88
IL recovery	19.95	5.51	23.69	5.29
Condensing	40.66	13.33	48.06	12.88
Cooling	0.78	0.22	0.93	0.21
Total Energy (MJ/kg HMF)	84.99	31.29	101.03	30.10

Table 5-7. List of price lists of the items for costing.

Item	Price	Reference
Raw Material		
Fructose	500 USD/tons	Novozymes 2009
MIBK	1890 USD/tons	ICIS 2009
IL	11000USD/tons	Our personal contact with the company
Catalyst	2000 USD/tons	Assumed
Process water	0.26 USD/tons	Novozymes 2009
Utilities		
Cooling water	0.022 USD/tons	Novozymes 2009
Electricity	0.0483 USD/kWh	Novozymes 2009
HP Steam (gas), 600 psig	14.23 USD/tons	Novozymes 2009
MP Steam (gas), 200 psig	16.04 USD/tons	Novozymes 2009
Other		
Waste water disposal	0.53 USD/tons	Peters et al[20].
Labor	28.13 USD/h	Peters et al[20].